S. Hrg. 107–619

# WHEN DIETS TURN DEADLY: CONSUMER SAFETY AND WEIGHT-LOSS SUPPLEMENTS

# HEARING

BEFORE THE

OVERSIGHT OF GOVERNMENT MANAGEMENT, RESTRUCTURING, AND THE DISTRICT OF COLUMBIA SUBCOMMITTEE

OF THE

COMMITTEE ON GOVERNMENTAL AFFAIRS
UNITED STATES SENATE

ONE HUNDRED SEVENTH CONGRESS

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# WHEN DIETS TURN DEADLY: CONSUMER SAFETY AND WEIGHT-LOSS SUPPLEMENTS

**WEDNESDAY, JULY 31, 2002**

U.S. SENATE,
OVERSIGHT OF GOVERNMENT MANAGEMENT, RESTRUCTURING,
AND THE DISTRICT OF COLUMBIA SUBCOMMITTEE,
OF THE COMMITTEE ON GOVERNMENTAL AFFAIRS,
*Washington, DC.*

The Subcommittee met, pursuant to notice, at 10:01 a.m., in room SD–342, Dirksen Senate Office Building, Hon. Richard Durbin, Chairman of the Subcommittee, presiding.

Present: Senators Durbin and Voinovich.

## OPENING STATEMENT OF SENATOR DURBIN

Senator DURBIN. I would like to welcome everyone to the hearing this morning. We will get under way, and I note people are still coming in. They are welcome to find a seat, since they are available. I would like to advise you that we anticipate some votes around 11 o'clock, so I am hoping that we can complete opening statements and the first panel. Then perhaps take a break for the voting, and return to complete the hearing.

I am pleased to welcome you to today's hearing before the Senate Subcommittee on Oversight of Government Management, focusing on "When Diets Turn Deadly: Consumer Safety and Weight-Loss Supplements."

There may be some argument across America about whether the great American pasttime is baseball. Last year nearly 50 million people attended a major league baseball game, but 100 million Americans are on a diet. It appears that we have spent a lot of our time as Americans thinking about weight loss. According to the Centers for Disease Control and Prevention, 25 percent of adult men, 40 percent of adult women, and an even higher percentage of teenagers are currently trying to lose weight. Some will be inspired by medical professionals to follow a diet and exercise. Others will be convinced by infomercials to buy the latest exercise video or magic machine. Many will look for a pill to help make the pounds disappear.

The purpose of this hearing is not to announce the new congressional diet or endorse the latest ab cruncher. The Federal Government should leave that to others. But there is one area of weight loss where the government, particularly the Food and Drug Administration, does have responsibility. Americans count on the FDA to make sure the drugs and nutritional supplements they take are safe. When it comes to drugs, the law is clear: no drug can be le-

gally sold in America until the FDA certifies it is both safe and effective. This certification involves extensive testing before a drug comes to market, and after it has come to market, monitoring of that drug and its consequences.

But when it comes to dietary supplements, everything from vitamins, minerals, herbal components, steroid precursors, animal derivatives and weight-loss supplements, we have a different standard. The Dietary Supplement Health and Education Act of 1994 said that in most cases supplements are considered safe. There is a presumption of safety. The product can be sold until the FDA can prove that it is unsafe.

Let me inject a personal note here, so that if there is any question in your mind. When I got up this morning, I took my vitamin. I believe in them. I think people should have the right to make that choice, to take the vitamins and minerals that they think are important to their personal health. We are not calling for the sale of vitamins by prescription. That is not what this hearing is about. But the reason that we are holding this hearing is because there have been several events recently, when it comes to dietary supplements, which have caught everyone's attention.

On January 9 of this year the Canadian Government issued a warning about a particular class of supplements containing the herb ephedra, sold for the purpose of weight loss. It is also sold for body building and to increase energy. The Canadian Government advised the people of Canada to avoid these products because they may, "cause serious, possibly fatal adverse effects," when combined with caffeine or other stimulants. They announced reports of adverse health events involving these drugs, which range from dizziness to tremors, headaches, irregular heart rates, seizures, psychoses, heart attacks and stroke. Health Canada then issued a voluntary recall of these products containing ephedra or ephedrine nationwide. Many of the ephedra supplements recalled by the Canadian health authorities can be found today on the shelves of stores across America.

Canada is not alone. A variety of athletic organizations including the International Olympic Committee, the National Football League and the National Collegiate Athletic Association have banned a variety of dietary supplements, including—and forgive me if I mispronounce this, I am a liberal arts lawyer—androstenedione, known as "andro" from this point forward in the hearing, a steroid precursor, and the weight-loss product ephedrine.

Despite this ban, a 2001 NCAA study of ergogenic compounds, compounds that increase work output, found that 4 percent of the 21,000 athletes that completed the confidential survey have used ephedrine in the past 12 months. Even more disturbing, this number had increased since the ban went into effect in 1997, especially among women's teams. According to the study most athletes reported using ergogenic products started in high school.

The obvious questions are these: Whether the health concerns announced by Canada and athletic organizations in our country about ephedra supplements are valid? What action should be taken by the Department of Health and Human Services and the Food and Drug Administration in light of the Canadian recall, and whether the 1994 law which Congress enacted, protects American

consumers from supplements that may be dangerous to their health?

At this hearing we will ask these and other questions about whether the 1994 law is working when it comes to weight-loss supplements. The GAO, General Accounting Office, will tell us about the analysis they just completed about the safety and regulation of this industry. The Inspector General's Office and the Department of Health and Human Services will tell us about a report they turned in on the warning system that exists for problems with dietary supplements, and we will ask the Food and Drug Administration whether the current system is working to protect Americans from dangerous health results. We will hear from a woman who took one of those supplements, with a very negative health consequence. We will hear from a doctor who studies weight loss. We will hear from a spokesman for the trade organization representing the supplement industry, as well as public health officials, who have attempted to increase the standard of supplement regulation in their State. I might add that some 21 States or more have imposed stricter regulation on the sale of these supplements than is required by the Federal Government.

To put this issue in some context, I want to first share some information on the supplement industry. There has been an explosion in the sale of dietary supplements since the 1994 law was enacted. As you can see from this slide,[1] the supplement industry is currently estimated to be on track to have $19 billion in sales in the year 2002. They have more than tripled their sales since the passage of the Federal law. Weight-loss products account for a significant part of supplement sales. So what do some of these weight-loss supplement manufacturers tell the consumers about their products? Here is an example of a supplement product produced by a company that has been in the supplement business for 20 years. I know it is a little hard to read, but it is a product called Pure Ephedrene. How is the consumer to distinguish between ephedra, which is marketed as an herbal product, and ephedrine HCl which is an over-the-counter drug, especially as ephedrine alkaloids are the active ingredients found in ephedra? I am not sure.

What kind of language is used to sell Pure Ephedrene?[2] Well, it says, "Pure Ephedrene is available all the time and in unlimited quantities, so you can have as much as you want whenever you want it." This is a strange claim for an all natural herbal product that is known to be a stimulant, especially given the fact that the safety range the industry claims for ephedrine alkaloids is 25 milligrams per individual dose up to a maximum of 100 milligrams a day, and the amount of ephedra per tablet in Pure Ephedrene appears to be 325 milligrams. Allow me to put this in perspective. The Canadian Government has said that they have a much different dosage level, 8 milligrams per dose, no more than 32 milligrams a day. If we read this warning label or advisory correctly in this particular advertisement, they are offering a product that offers in one dose 10 times what the Canadians say is a safe daily dose in four separate dosages.

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[1] The slide appears in the Appendix on page 77.
[2] The slide appears in the Appendix on page 78.

The next slide is an example of a current warning label on a top-selling weight-loss product containing ephedra and caffeine.[1] And here is what it says: "This product is for adult use only, and should not be used by pregnant or nursing women or by anyone with any known medical condition." What does that mean? What does it mean to the consumer? While ephedrine and caffeine combinations were banned by the FDA in 1983 for over-the-counter medications, many weight-loss supplements contained ephedra and some herbal form of caffeine, the combination, incidentally, which the Canadians have found to be highly dangerous.

I am looking forward to our witnesses to help us understand this issue and the responsibility we have to protect the health of American consumers, and at the close of the hearing I will make an announcement concerning some action which I believe that we should be taking on Capitol Hill.

Let me at this point welcome the first panel of witnesses. Janet Heinrich is the Director for Health Care—Public Health Issues with the General Accounting Office. Her office has produced several reports relating to dietary supplements, including a recent report titled "Health Products for Seniors, Potential Harm from Anti-Aging Products." I am going to look for that one too.

Second is Dr. Michael Mangano. He is the Principal Deputy Inspector General within the Office of the Inspector General for the Department of Health and Human Services. Thank you.

Finally, Joseph Levitt, who is the Director of the Center for Food Safety and Applied Nutrition within the Food and Drug Administration.

We thank you for coming this morning. It is customary for the Subcommittee to swear in all witnesses. Therefore I would like to ask you to stand and please raise your right hand.

Do you swear that the testimony you are about to give is the truth, the whole truth and nothing but the truth, so help you, God?

Ms. HEINRICH. I do.

Mr. MANGANO. I do.

Mr. LEVITT. I do.

Senator DURBIN. Let it be noted for the record that the witnesses answered in the affirmative. We have your statements, and I have a number of questions which I would like to ask, and I would ask you if you would please summarize your statements in about 5 minutes. We will not hold you to that exactly. And then I will proceed with some questions.

Ms. Heinrich, would you like to start?

## TESTIMONY OF JANET HEINRICH,[2] DIRECTOR, HEALTH CARE—PUBLIC HEALTH ISSUES, U.S. GENERAL ACCOUNTING OFFICE

Ms. HEINRICH. Mr. Chairman, I am pleased to have the opportunity to testify as the Subcommittee considers concerns about dietary supplements that are used for weight loss.

As you said, U.S. sales of weight-loss supplements have increased steadily. It is estimated that Americans spent almost $2

[1] The slide appears in the Appendix on page 81.

[2] The prepared statement of Ms. Heinrich with attachments appears in the Appendix on page 40.

billion in weight-loss supplements in 2001. Obesity in the United States is reported to be a growing epidemic, and many people are trying to lose weight.

As sales of weight-loss supplements have increased so have concerns associated with their marketing and use. Because of these concerns, you asked us to examine the safety and efficacy of weight-loss supplements, Federal oversight, research, and public education efforts, and State and local regulatory efforts aimed at consumer protection of these products.

For most weight-loss supplements there is little scientific evidence to support their efficacy. Although there have been studies on specific ingredients, many of these studies were of short duration, involved small numbers of individuals, or use study approaches that limit the usefulness of their findings.

There has been limited Federal research on weight-loss supplements. The Office of Dietary Supplements at the National Institutes of Health is working with other Federal agencies to develop a research agenda. However, none of the institutes and centers have made weight-loss supplements a priority at this time. Available research, again limited, also suggest that some supplements are associated with harmful side effects. Some side effects are minor, such as indigestion or rash, while others are very serious. For example, DHEA, a hormone associated with reduction in fat deposits may increase the risk of breast cancer. And ephedra, as you suggest, has been associated with seizures, heart attacks, and stroke. Supplements also may be contraindicated for individuals with certain medical conditions or may have dangerous interactions with prescription and over-the-counter drugs.

The amounts of active ingredients can vary from what is indicated in a product label. Products sometimes contain ingredients not listed on the label, or may have as many as 22 active ingredients, all listed on the label, but with amounts unknown if the product contains a proprietary blend. Studies have also found supplements contaminated with pesticides or heavy metals known to damage the liver and kidneys.

The Food and Drug Administration, FDA, and the Federal Trade Commission, FTC, have oversight responsibilities for safety and marketing. FDA has been hindered in its ability to address safety concerns with weight-loss supplements by weaknesses in its Adverse Event Reporting System, as well as the lack of scientific evidence from clinical trials.

Senator DURBIN. Can I interrupt you for a second? Would you explain what Adverse Event Reporting means?

Ms. HEINRICH. What that means is that on a voluntary basis, individuals or health care providers, can turn in information about medical conditions that they think are associated with a particular product. FDA has an Adverse Event Reporting System for all drugs as well as for dietary supplements.

Senator DURBIN. Thank you.

Ms. HEINRICH. Difficulty in obtaining and properly documenting these voluntary Adverse Event Reports has been a major problem in the past. Even with Adverse Event Reports, FDA's ability to respond is different for dietary supplements than for drugs. Dietary supplements are regulated more like foods, and FDA must meet a

higher safety threshold to take regulatory action than for drugs that contain similar ingredients. While it is reasonable to assume that foods are safe, many supplements are more like synthetic drugs.

FDA and FTC have taken enforcement actions against manufacturers for improper labeling and false advertising. FDA has taken 16 actions since 1995 against manufacturers of dietary supplements marketed with weight-loss claims almost entirely for products that are improperly labeled as dietary supplements. For example, in 2001 FDA took action against the manufacturer of AMP II Pro drops, an unapproved drug product that contained ephedrine for a non-herbal source, but was labeled as a dietary supplement. FTC has taken legal action in 30 cases involving weight-loss substances in this time period. For example, in 2000 Enforma Natural Products agreed to a settlement with FTC regarding the products Fat Trapper and Exercise in a Bottle for deceptive claims such as "You can eat what you want and never have to diet again."

FDA does have authority over good manufacturing practices, the GMPs, which could help in oversight of product dosage and contamination issues. FDA drafted GMP regulations for dietary supplements in 1997, but has been slow to finalize these regulations. GMPs would standardize manufacturing, packaging and holding practices, and improve FDA's enforcement capabilities since the law provides that dietary supplements not manufactured under conditions that meet GMPs would be considered adulterated.

In summary, Federal activities related to weight-loss supplements have focused on oversight of marketing more than safety. Federal activity has focused less on safety in part because of the lack of scientific evidence and the weaknesses in the voluntary reporting system for adverse events. For FDA regulatory action there is a different standard of proof requiring a determination that a supplement causes significant or unreasonable risks. Further research on the efficacy and safety of dietary supplements is needed to guide consumers choice, especially as the upward trend in sales and use is expected to continue.

Mr. Chairman, that completes my statement. I am happy to answer any questions.

Senator DURBIN. Thank you. Mr. Mangano.

**TESTIMONY OF MICHAEL F. MANGANO,[1] PRINCIPAL DEPUTY INSPECTOR GENERAL, OFFICE OF INSPECTOR GENERAL, DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Mr. MANGANO. Thank you, Mr. Chairman. I appreciate this opportunity to share with you the results of the work we have done on taking a look at the FDA's Adverse Event Reporting System for the dietary supplements.

Unlike prescription drugs, the FDA lacks the authority to require dietary supplements to undergo premarket approval for safety and efficacy. Rather, they have to rely extensively on the Adverse Events Reporting System to give them signals of product problems with consumer safety. Our review found, however, that the Adverse

[1] The prepared statement of Mr. Mangano with attachments appears in the Appendix on page 65.

Event Reporting System for dietary supplements was inadequate as a safeguard to protect consumer safety. We believe it is so because it has three major weaknesses. The first, the system detects relatively few adverse events. Like most Adverse Event Reporting Systems, it is a passive system, requiring somebody with an adverse event to link that event with the use of a dietary supplement and then report it to the appropriate authorities. Our study confirmed an earlier review that the FDA commissioned, which found that very few adverse events are ever reported for dietary supplements.

In our study we found that from 1994 through 1999, only a little over 2,500 adverse events had ever been reported relating to dietary supplements. As a comparison, in the year 1999 the Food and Drug Administration received about 460 adverse events on dietary supplements. Over the same time period, the same year, the Poison Control Centers received over 13,000 reports related to dietary supplements.

The second weakness the FDA has with its Adverse Event Reporting System is its difficulty in generating signals that there may be a public problem with regard to a particular dietary supplement. The FDA lacks sufficient information such as consumer medical records, product ingredients and the identity of manufacturers so as to analyze the reported events and determine if they raise concerns regarding the public health.

For example, we found that FDA could not obtain medical records for over half of the Adverse Event Reports where they had actually requested those records. With regard to product information, FDA was unable to determine the ingredients of one third of the dietary supplements that were indicated in an Adverse Event Report, and they had no product label information for three-quarters of the supplements that appeared in those Adverse Events Reports.

So the agency really needs those labels in order to determine the supplement ingredients and whether they should take action in the future. Manufacturers have information that would also be very important for FDA to have regarding these supplements, yet they could not identify even the manufacturer for one-third of the products in the Adverse Events Reports. Finally, the database housing the Adverse Event Reports was wholly inadequate for analysis purposes.

The third weakness of the Adverse Event Reporting System is that sufficient information is not available to assess whether action is actually required by the FDA to protect public safety. FDA relies very heavily on clinical research, scientific literature and laboratory testing to assess signals generated by the system, but because supplement manufacturers are not required to conduct those clinical trials, little of this information is actually known.

The FDA lacks information on the size of the consumer population actually taking the dietary supplements and the dosage amounts they're taking. And as mentioned earlier, they suffer from too few Adverse Event Reports, inadequate Adverse Event Reports, and a limited computerized database to help them facilitate the analysis of that data.

We estimate that FDA's taken about 32 actions between 1994 and June 2000, and the two most common were voluntary product recalls and warnings to consumers.

We recognize, however, that FDA faces significant legislative and resource barriers to improving the Adverse Event Reporting System.

Our report offers a number of recommendations. I'll highlight just a few here this morning. We believe that FDA should seek authority to require manufacturers to report serious adverse events for some products, require manufacturer and product registration, contract with the Poison Control Centers to obtain their data and develop a new computerized database that helps track and analyze Adverse Event Reports.

I am pleased to say that FDA has recently reported to us that they have taken a number of those recommendations and put them into action.

Mr. Chairman, millions of consumers take supplements every day without any apparent problems and do receive health benefits. However, risks do exist, and the consumers need to be protected.

This completes my oral testimony. I will be happy to answer any questions at the appropriate time.

Senator DURBIN. Thanks a lot.

Our next witness is Joseph Levitt with the Food and Drug Administration. Please proceed.

**TESTIMONY OF JOSEPH A. LEVITT, ESQ.,[1] DIRECTOR, CENTER FOR FOOD SAFETY AND APPLIED NUTRITION, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY DR. CHRISTINE LEWIS TAYLOR, DIRECTOR, OFFICE OF NUTRITIONAL PRODUCTS, LABELING AND DIETARY SUPPLEMENTS (ONPLDS), CENTER FOR FOOD SAFETY AND APPLIED NUTRITION (CFSAN), AND JOHN TAYLOR, DIRECTOR, OFFICE OF ENFORCEMENT, OFFICE OF REGULATORY AFFAIRS (ORA), FOOD AND DRUG ADMINISTRATION (FDA)**

Mr. LEVITT. Thank you very much, Mr. Chairman. It's a pleasure to be here. Let me first introduce two colleagues that are here with me. The first is Dr. Christine Taylor, Director of our Office of Nutritional Products, Labeling and Dietary Supplements in the Center I direct. And the second is John Taylor, Director of the Office of Enforcement, Office of Regulatory Affairs at the FDA level, so he has responsibility across all the regulated products.

I would summarize my testimony, Mr. Chairman, with five main points. Point No. 1, with which I think everybody here will agree, is that dietary supplements present a significant challenge worthy of our attention. As you pointed out, Mr. Chairman, in your opening statement, there is widespread use in this country of dietary supplements, clearly increased since passage of DSHEA in 1994, and DSHEA looks to FDA to step in if there is a problem and to be vigilant on behalf of the public. We welcome reports from GAO, IG, and others that can help us meet this challenge.

[1] The prepared statement of Mr. Levitt appears in the Appendix on page 86.

Point No. 2 is we do have a plan. We spent, in fact, an entire year developing a strategic plan on how we would implement DSHEA. I have a copy here, and copies have been provided to the Subcommittee. The goals of this plan are clear. We need to fully implement this law. In doing so we need to provide consumers with a high level of confidence in the safety, composition, and labeling of these products. We need to do so in a science-based way, consistent with all of FDA's successful programs, and we need to recognize that implementation of this law is going to take sustained time and effort.

Now, we developed this plan with broad public import and support. The major theme we heard from stakeholders was safety first. As you've already heard, look at the Adverse Event Reporting System, make it functional, develop good manufacturing practices, get them implemented, but I will also tell you that fundamentally, long term, this program will not be successful unless there is a much stronger scientific underpinning to the products, and I think that has been reinforced by both speakers already.

Point No. 3. Congress has asked us what it would take resource-wise to implement the strategic plan, and I am pleased to say that we submitted a report to Congress this past May which outlines that. That report concludes that our needs would be in the range of $40 to $65 million over 5 years. That would be compared to $9 million that we had allocated in fiscal year 2002, the current fiscal year we're in. The plan also describes how we would prioritize those resources, how we would implement them over time, starting with safety issues, moving on to inspectional issues, and so forth. I think the bottom line is, you'll agree, that it does take time, money and people to operate and implement an effective program.

Point No. 4. We are making progress, admittedly incrementally. Each year across our entire center we publish our annual priorities for what we accomplish, or intend to accomplish that year. One section of that report includes dietary supplements. And at the end of each year, we publish our report on what we have been able to accomplish, and we have been averaging a good 85 to 90 percent completion rate of what we set out to accomplish. We're also pleased that Congress has started to appropriate funds earmarked for dietary supplements. We've received funds recently in the area of Adverse Event Reporting and academic collaborations on the science-based and on enforcement, and we are seeing progress in each of these areas. We also were able to fund a study to be conducted by the National Academy of Sciences Institute of Medicine to develop a framework for evaluation of the safety of dietary supplements, and you may have seen some press this week on an interim report from that group. My testimony also outlines a number of enforcement actions which we have taken.

Point No. 5 though, again of which I think every speaker will agree, we have a lot more to do in this area. As just one example, on the product ephedra that you have mentioned, Secretary Tommy Thompson issued a statement in June which outlined a two-prong approach. Prong one is that we need better research. There is an ongoing evidence-based review being conducted by the Rand Corporation under the auspices of the NIH to determine what is known about ephedra and what research needs to be done, and

that the NIH is committed, the Department is committed to using that report as a guide to future research needs.

Concurrently FDA has already initiated a number of enforcement actions against products that are synthetic ephedrine, and therefore they're not botanical and they fall outside the scope of DSHEA.

Summarizing then and wrapping up with my five main points, dietary supplements, of which weight-loss supplements are an important part, and probably illustrative of the broader group of herbal supplements at large, presents significant challenges, something we clearly need to devote our attention to. Point 2 is that FDA has developed a strategic plan on a blueprint of how we would implement this with broad stakeholder import and support. No. 3, we thank Congress for asking for our funding needs, and we have issued that report. No. 4, we are making incremental progress consistent with the resources that have been allocated. And No. 5, we recognize this as a long-term effort. There's a lot more we have to do. We welcome the input you have, the visibility this hearing provides to helping us achieve those goals.

Thank you very much, Mr. Chairman. I know in your letter of invitation you had a number of specific questions, and I'll be happy to try and answer those during the question period.

Senator DURBIN. Great. Let us start with a few questions, and some of these are very basic, but I think we ought to put them on the record.

From the Food and Drug Administration's viewpoint, is it safe to say that the chemical properties of ephedrine can be found in a variety of ways in both natural, botanic sources as well as synthetic sources?

Mr. LEVITT. That's right.

Senator DURBIN. And is it also true that the Food and Drug Administration, over the years, has regulated the synthetic sources of ephedrine and how they can be sold in America?

Mr. LEVITT. Yes.

Senator DURBIN. For prescription drugs as well as over-the-counter?

Mr. LEVITT. Yes.

Senator DURBIN. Is it also true that when it comes to the combination of ephedrine with, for example, either a stimulant or an analgesic, that there have been limitations on the products that can be offered for sale as prescription drugs and as over-the-counter products?

Mr. LEVITT. I think any product that is regulated as a pharmaceutical, whether it's as a prescription or as an over-the-counter drug under our monograph system, regulated by another part of FDA, not the part I direct, that there are boundaries associated with claims, with dosages and so on and so forth.

Senator DURBIN. But in terms of the limitation of sale, are there any forms of ephedrine that have been prohibited by the FDA from sale, either as an over-the-counter drug or as a prescription drug?

Mr. LEVITT. Well, the history is such—I'm not sure I can answer that with the specificity you're looking for—but any time there's a monograph that lists the boundaries, and so anything outside that boundary is not permitted.

Senator DURBIN. And so from the consumers' point of view, if the Food and Drug Administration has decided that when ephedrine is in a drug, a prescription drug, or in an over-the-counter product, that it has to have some limitations in terms of how it can be prescribed and dosage and that sort of thing. From the consumers' point of view, that same drug could be available through a supplement in a botanical form without the FDA limitations.

Mr. LEVITT. The one distinction I would draw, as we have pointed out, if an ephedrine product is a synthetic-derived product, then that product is not permitted to come under the dietary supplement provisions. Ephedra comes under the part of the definition of dietary supplements for botanicals.

Senator DURBIN. Understood.

Mr. LEVITT. So if there is synthetic derived—and I think you'll find that a lot of the pharmaceutical products that you're referring to are synthetic derived——

Senator DURBIN. I understand that. This is really basic. I go into my neighborhood drugstore in Springfield, Illinois, and I look at the pharmacy and I look at what is on the shelf. And I know that if I am going to get some form of ephedrine through a prescription drug, I need a doctor's prescription, and the pharmacy will fill it with instructions on how I am to take it.

Mr. LEVITT. Right, for certain uses.

Senator DURBIN. I also know if there is an over-the-counter drug for sale there, according to the FDA, it is going to have instructions on the back of it as to dosage, contraindications, warnings and that sort of thing.

Mr. LEVITT. That is correct.

Senator DURBIN. If I move——

Mr. LEVITT. There is now a new standardized format for that which is very good.

Senator DURBIN. Then I move to the third counter and I see a dietary supplement. It contains the same drug. Maybe it is called ephedra, maybe it is ephedrine, but it contains the same drug, but what is on the label of that product as a matter of warning or recommended dosage is really not determined by the Food and Drug Administration. That is determined by the manufacturer of the product.

Mr. LEVITT. That is correct.

Senator DURBIN. OK.

Mr. LEVITT. That is because, as you pointed out in your opening statement, when Congress passed the law there was a presumption that these were natural ingredients with a history of safe use, and therefore, that was an appropriate way for them to be marketed.

Senator DURBIN. But if you blindfolded a chemist and walked him in and said, "I have got ephedra or ephedrine coming at you in three different forms," it is still that drug, whether it is from a botanical source or from a prescription drug or from an over-the-counter, it is still that basic chemical compound coming into your body?

Mr. LEVITT. There are clear similarities.

Senator DURBIN. Now, when it comes to the manufacturing practices of these drugs and over-the-counter products and supplements, I understand the Food and Drug Administration monitors

very carefully how drugs are manufactured in terms of foreign matter as Ms. Heinrich and others have said, and in terms of its purity. The same thing would be true for over-the-counter drugs, is it not?

Mr. LEVITT. Yes.

Senator DURBIN. But when it comes to dietary supplements, what standards, when it comes to manufacturing practices, would the FDA impose on the supplement industry?

Mr. LEVITT. Well, the law does explicitly authorize FDA to issue good manufacturing practice regulations. We did issue, some years ago, what's called an advance notice of proposed rule making. We do have a proposed rule which we hope to get out very shortly that would elicit public comment, but really take us a major step towards getting those kinds of regulations in place. Again, I think there was a broad support for getting those kinds of regulations in place. Everybody recognizes the need for them.

Senator DURBIN. I have been around Washington long enough to know that things do take some time, but we are talking about a 1994 law, are we not?

Mr. LEVITT. That is correct.

Senator DURBIN. And we are talking about the fact as we sit here today in 2002, we are talking about public hearings on good manufacturing practices for dietary supplements.

Mr. LEVITT. That is correct.

Senator DURBIN. They have not been established?

Mr. LEVITT. Yes, correct.

Senator DURBIN. The products that are currently on the market, the dietary supplements, for example, that are currently on the market are not being manufactured according to any standards that have been established by the Federal Government or the Food and Drug Administration?

Mr. LEVITT. That is right.

Senator DURBIN. It is up to——

Mr. LEVITT. That's why we think it's important to do it.

Senator DURBIN. I think it is too. That is why it is really up to every individual manufacturer to call their own standards, call their own shots in terms of what they put in that bottle and how they label it.

Mr. LEVITT. At this point in time, that is correct.

Senator DURBIN. And, Ms. Heinrich, what have you found, as you have looked into these products?

Ms. HEINRICH. Well, certainly the reports in the literature are that there is contamination, that there is variability in terms of the dose, that you can't assume that what the label says is what you'll find in the product. And the other area that is of growing concern is the fact that many supplements, the dietary supplements for weight loss especially, have multiple ingredients, as I said, up to 22 ingredients, and they may not—you may not have the information about what dose is in the product.

Senator DURBIN. Mr. Levitt, I mentioned in the opening statement the action taken by Canada, which basically has recalled these products, ephedrine products, particularly those combined with a stimulant, and said that they are a danger, and they are very explicit in terms of the danger that they see here, in terms

of heart attack, stroke, psychotic episodes, seizures. What kind of notice does the FDA take of that action in Canada; what kind of reaction has the FDA had to that Canadian decision?

Mr. LEVITT. I think there were two reflections upon that action. No. 1 is that action closely resembles a proposed regulation that FDA issued several years ago, and therefore is consistent with some of the steps FDA historically has sought to take.

No. 2, as I understand the Canadian framework, they have a different legal framework, and that these products are generally not lawfully available in the country as they are here. And so they're operating within a different framework, but actually looking to this country for what actions have been taken in the past.

Senator DURBIN. Well, I do not quarrel with that. I understand that our 1994 law is different from the Canadian law. But what I am asking for is not from the legal interpretation, although I know you come to this as a lawyer, but I am looking from the medical and scientific side. If we have a neighbor to the north which is considered very similar to the United States in its culture and values, which shares our pharmaceutical products on a regular basis because of the trust we have engendered between the two countries, and they have taken a product which we have for sale in drug stores and nutrition stores across America, and announced that it is unsafe for Canadians, so unsafe that they recalled it from the shelves, what I am really driving at is from the medical and scientific viewpoint, did that not raise a red flag at the FDA that perhaps we are not moving quickly enough or not taking this concern seriously?

Mr. LEVITT. Well, let me read to you from the HHS press release of June 14, which I think speaks directly to that point. It says very clearly, and I quote from our deputy commissioner, "These products are not for everyone." "Consumers should read labels carefully to ensure their proper use." It goes on to state that consumers should not use these products if they are under the age of 18 or if they are pregnant or nursing women. It further states that adult consumers should consult health care providers prior to use of such products if they have current or previous history of high blood pressure, heart or thyroid disease, a seizure disorder, depression, diabetes, difficulty urinating, prostate enlargement, glaucoma, or are using any prescription drugs. It goes on to alert consumers that this is a product we have concerns about, and that consumers should be vigilant as they take these products for possible side effects, and that specifically, "Consumers should discontinue use if any of the following symptoms are experienced: Rapid or irregular heartbeat, chest pain, severe headache, shortness of breath, dizziness, loss of consciousness, sleeplessness or nausea."

So I think that we clearly have recognized some of the potential concerns with this product, have tried to alert consumers to that, and we reinforce that message whenever possible, and I thank you for the opportunity to reinforce that today.

Senator DURBIN. Well, I am glad you did reinforce it. With all due respect, that is a press release, is it not?

Mr. LEVITT. Yes.

Senator DURBIN. Yes. And I do not know how many people read it when you issued it, but when I go into my corner drugstore in

Springfield and buy a dietary supplement with ephedra in there, am I going to find that warning on the label?

Mr. LEVITT. You will find a number of warnings that are voluntarily put on by the manufacturers, and they tend to be of the first kind of language I read on the kinds of consumers that should avoid using the product or consult a physician before using the product. But that is consistent with what you'll find on a lot of products.

Senator DURBIN. But it is a voluntary label.

Mr. LEVITT. That is correct.

Senator DURBIN. We have seen some disclosures already that do not get even close to the warnings which you have just outlined, which are lengthy. It sounds like the end of one of these ads on television about the little purple pill. But what I am saying to you is it is voluntary, and from a consumers' viewpoint, unless you happen to be on the mailing list from the FDA and got a copy of that press release, you may never see the warnings which you have laid out here; is that not correct?

Mr. LEVITT. It is correct that the warnings are voluntary, and we do try to get this message out as broadly as we can.

Senator DURBIN. Let me ask you about the dosage level if I can, and we apparently have some difference of opinion between the United States and Canada as to safe dosage, and I might go further to say that when you look at the actual products being sold, it appears that some of the companies are paying little or no attention to either standard as announced. Is there a safe dosage standard for products containing ephedrine supplement products that the FDA has announced?

Mr. LEVITT. Let me share with you the brief history on this subject. In the earlier part of the 1990's, FDA had a Public Advisory Committee meeting addressing the safety of ephedra products, and the recommendation of the Advisory Committee was to see if FDA could determine a safe dose or an acceptable dose. FDA went back to the existing body of information that the agency had, which was the Adverse Event Reports, and used those reports as best as we could, consistent with what's known in the literature and about the product in general and proposed a dose level. A study was done following that by the General Accounting Office. I will let them speak if I say anything incorrectly and correct. But their conclusion was that those Adverse Event Reports, while important in signalling a potential problem with this product, were not designed to establish a dose level, and it was not appropriate to use them for that purpose. And so where we stand today is that we don't have a good scientific foundation—goes back to my opening comments—a strong scientific foundation. We don't have a strong scientific foundation establishing what is the best dose to use.

Senator DURBIN. We certainly do not, and I think the conclusion from your statement is the following: The Food and Drug Administration since 1994 has not established a standard for safe dosage of this product.

Mr. LEVITT. That is correct.

Senator DURBIN. The Canadians have reached a conclusion that resulted in their withdrawal of this product from sale in Canada, and we have seen other actions taken by other organizations, but

our government has not taken an action to either withdraw the product or even to establish a safe dosage. Is it not also true that the American Medical Association, after this Canadian action, wrote to the Food and Drug Administration and made a recommendation concerning ephedrine products?

Mr. LEVITT. They have written to us.

Senator DURBIN. Do you recall what they asked?

Mr. LEVITT. In an earlier letter I believe they recommended that the products be removed from the market.

Senator DURBIN. Letter of January 28, 2002 to Dr. Bernard Schwetz, and this is from Dr. Michael Maves of the American Medical Association, first sentence, "On behalf of the American Medical Association, I am writing to reiterate our call for the Food and Drug Administration to initiate proceedings to remove dietary supplements containing ephedrine alkaloids from the United States market." He goes on to spell out the reasoning based on Adverse Event Reports, and they are concerned about the danger of this product as against its value to the American consumer.

The point I am getting to, Mr. Levitt, is it appears that the evidence keeps piling on to the Department of HHS and FDA about the danger of this product, and as you come today to testify, 8 years after the law has been passed and as this evidence accumulates, it appears that nothing has been done. The proposed rules are good and we will talk about when they might come about but from the consumers' viewpoint, neither a required warning label, an established dosage, or any consideration as to whether some of these products should be removed from commerce, none of this has been taken despite the clear danger that was perceived in Canada when it made this decision.

Now, is this for lack of resources at the FDA? Is it because your hands are tied by legislation, or is there some other element at work here?

Mr. LEVITT. It is because the data are not—there's not a consensus on the clarity of the data to the point that you describe. We held a public meeting with government officials on the panel a couple summers ago—I guess it was 2 years ago by now—and the outcome—and we presented all the Adverse Event Reports; we brought our consultants. Some of the people testifying today testified at that meeting. The report coming out of that meeting reinforced that the Adverse Event Reports generate a strong signal, but we did not have the kind of stronger clinical data that they would like to have seen. We took that to the NIH and they commenced what they call—because we said if we need more research, then we need it—and what they call an evidence-based review. That is what was in the HHS press release of June 14.

Senator DURBIN. Which we are hoping some consumers saw. Let me ask this——

Mr. LEVITT. We are hoping it will result in firm recommendations and identification of the research we need to get to the bottom of it.

Senator DURBIN. Well, I hope you get to the bottom of it soon too because you have had over 1,000 Adverse Event Reports which led the AMA to say take this product off the shelf. Mr. Mangano has made it clear—and I will return to him and ask this question—the

Adverse Event reporting for supplements in this country is woefully inadequate because it is voluntary. 13,000 adverse events were reported to the Poison Control Centers in the year 1999 for dietary supplements, and only 460 or 480 were reported to the FDA. So clearly, this system of reporting is not giving the information from consumers to the industry to the FDA for them to make a decision. And when we hear Mr. Levitt and the FDA say, well, we just do not have enough information from Adverse Event Reports, this is circular, and frankly, it is leading to some disastrous results.

Mr. Mangano, you have talked about changing this Adverse Event reporting system. Would you comment on that?

Mr. MANGANO. Sure. The system itself is inadequate as a system to collect data. I'm talking about the computerized system that actually houses all of the events reports themselves. It was not a system that could either house all the information or be used fully in terms of analyzing the necessary information. So that needs to be changed. I know that FDA has put about $2.5 million into that process itself, but there are a whole lot of other things that have to go on at the same time. The voluntary system just is not going to work for the kinds of products that can cause risk through human consumption.

We need to have reporting by the manufacturers of what the ingredients are in their individual products. We need to have mandatory reporting by the manufacturers of adverse events for some products, products like ephedrine, that could cause problems. Right now it's voluntary. We need to complete the good manufacturing practice standards, etc.

They need to learn a little bit more from the Poison Control Centers about the kinds of information they're getting from that source. They need to do all the kinds of research that Dr. Levitt has just talked about.

The resources haven't been there in the past for them, but they need to really try and ratchet up developing the clinical studies that will help them when they do get a signal that there might be something wrong with a product. They need to have the clinical research that's available to them to tell them whether they need to act on it immediately.

So those are just a few of the things that need to happen.

Senator DURBIN. Ms. Heinrich, the GAO and the Inspector General have both looked into this Adverse Event Report situation here, and I would like to ask you what role do you believe that this adverse event reporting should play in protecting consumers from potentially harmful weight-loss supplements?

Ms. HEINRICH. I think we have to be very thoughtful about the design of this Adverse Event Reporting System. The fact of the matter is you have to have good and complete data going into the system. Then you have to have people that are able to look at those events and decipher patterns or early warning signals that there may be a problem. And then you have to have the ability to go further where there is a problem and do thorough investigations and be able to link the clinical outcomes to the ingestion of one of these dietary supplements.

The problem is that it is voluntary. In this instance industry, manufacturers are not required to report adverse events that they know about, and so with dietary supplements, you don't have complete information on which to determine these patterns.

More to the point, when FDA does see a pattern as they have said that they see in ephedrine, for example, they really have a higher threshold of evidence that they have to have in order to prove harm and possible public health safety concerns.

Senator DURBIN. I guess, Mr. Levitt, that is a point I am going to come to here, and maybe that is a question for the FDA. I know there are many doctors who work the FDA, and I do not believe you are a medical doctor?

Mr. LEVITT. That is correct.

Senator DURBIN. I am not either. But—and I do not play one on TV, even on C–SPAN. But I would say to you that it would seem that the first obligation of the Food and Drug Administration is to protect American consumers. When in doubt, err on the side of protecting American consumers. We have a situation here where you have said the FDA just cannot reach a conclusion on warning labels, on dosage and the like, because we just do not have enough information. We do not have enough statistical data on Adverse Event Reports. We know the system is stacked against you. The law that was passed in 1994 makes those reports voluntary. The industry is not rushing to your door to saying, "Oh, listen, there are some more reports on bad outcomes with our product." In fact, they are holding back on that information. And so you do not have the information to deal with. The Poison Control Centers are learning a lot more than the FDA. What is wrong with this picture? And so you do not have the statistical information coming in to make an ordinary decision about how to protect American consumers, but you do know something. You know that the Canadians have come to the conclusion already that this is unsafe to be sold in their country. You know as well that 21 States or more have established stricter standards than the Federal Government when it comes to the sale of these products. You know as well that the American Medical Association, which is not considered a fly-by-night operation, has notified the Food and Drug Administration that there is a real danger in the sale of these products. You know that three football players dropped dead after taking these supplements and the NFL has banned it, as well as the International Olympic Committee and the NCAA.

When all of this accumulates, does not the Secretary of Health and Human Services come to the conclusion that I should err on the side of protecting Americans? These products are killing people and hurting people, and we should err on the side of helping them, rather than waiting for statistical evidence which by this law will never appear.

Mr. LEVITT. Mr. Chairman, we agree with you that in this product area in general, this product in particular, is an area that we need to be doing more.

Senator DURBIN. This has been 8 years.

Mr. LEVITT. We agree that our Adverse Event Reporting System needs to be upgraded. We're in the process of doing that. We thank you for the funds to do that. I also want to reinforce a point made

by my colleagues. The Adverse Event Reporting System needs to be an effective tool for an early warning of problems, but that early warning system, once a problem or potential problem is identified, needs to be complemented with a broader, stronger, scientific foundation of information. We will continue to search for ways to get that information, and to meet our responsibilities under the law as best as we can.

Senator DURBIN. I do not want to assign the blame to you personally, and I do not. I do not necessarily want to assign it to the FDA because I respect this agency more than you can imagine. But either the law is bad, the resources are not being given to you, or there is no will to deal with a clear threat to the American consumers. It may be all three. I hope not. And I hope that we can make some steps to resolve it.

Now, let me ask you about one particular bill before I draw this panel to a conclusion. When we passed the Bioterrorism Bill, we called for the registration of food manufacturers, distributors and importers. So can I conclude from that that at least now the most basic information about the identity of supplement manufacturers will now be available to the Federal Government?

Mr. LEVITT. That is correct. Dietary supplement manufacturers are clearly included under the law. In fact we had our first outreach meeting with industry in general on these provisions just yesterday. A number of dietary supplement representatives were there. And I think everybody accepts and recognizes that as a very positive step.

Senator DURBIN. Now, let me also add, too, is it not a fact that some businesses within the supplement industry have tried to create their own code of good conduct and manufacturing practices to try to establish some standards that have not been imposed by the government?

Mr. LEVITT. That is correct.

Senator DURBIN. But there are some companies that are not part of that code.

Mr. LEVITT. That is correct also.

Senator DURBIN. Well, this raises another question as to whether or not the industry itself perceives a problem. Can any of the witnesses at this table testify about the question of lawsuits and claims against the supplement industry? Did that come up during the course of the GAO investigation?

Ms. HEINRICH. We did indeed try to document the types of claims that have been filed, and there are several. And certainly ephedra is involved in several lawsuits. You've had claims brought by State Attorneys General, and then you have also had liability claims from individuals.

Senator DURBIN. Thank you.

If there is anything else that any of the panel members would like to say at this point, I will give you this opportunity. If not, thank you very much for your testimony. I appreciate it.

I think we will go ahead and bring on the second panel. We may have to interrupt it if there is a vote. Let me invite Cynthia Culmo, who is Chairperson for Drugs, Devices, and Cosmetics with the Association of Food and Drug officials in Austin, Texas; Dr. Steven Heymsfield, Deputy Director at the Obesity Research Center, St.

Luke's-Roosevelt Hospital Center, Professor of Medicine, Columbia University, College of Physicians and Surgeons in New York; Michael McGuffin, President of the American Herbal Products Association from Silver Spring, Maryland; and Karen Ruiz, a consumer from San Clemente, California.

As you probably noted before, we do ask our witnesses to take an oath, and if you will please stand.

Do you solemnly swear the testimony you are about to give is the truth, the whole truth and nothing but the truth, so help you, God?

Ms. CULMO. I do.

Dr. HEYMSFIELD. I do.

Mr. MCGUFFIN. I do.

Ms. RUIZ. I do.

Senator DURBIN. Let the record indicate that all four of the witnesses answered in the affirmative, and we will start with testimony.

And let me begin with Mrs. Ruiz. Thank you for joining us from California today. We have your statement for the record, and if you would like to give us a summary of your experience for the record, I would appreciate that.

## TESTIMONY OF KAREN RUIZ,[1] CONSUMER, SAN CLEMENTE, CALIFORNIA

Ms. RUIZ. This is amazing, and I want to thank you for having me here. Senator Durbin, I would like to thank you for taking the time to hear my testimony, and it is my hope that by sharing with you that others will be spared the serious and life-changing effects of taking unregulated diet supplements, specifically containing ephedra and guarana.

I would like to just read to you a journal entry I wrote. I grabbed this at the last minute. But it's impacted my life, it's impacted it a lot, and I wanted to read this to you. I wrote: "I'm 32-years-old now and determined to journal a lot more consistently. Today I feel good. About 4 months ago I had my third manic episode. It baffles me how my mind can completely take me to non-reality and I am completely helpless when it happens. It just happens. And when it does, it seems so wonderful and perfect, and everything seems to come together and make such perfect sense. But always only to me. Once Donny, my husband, realized I was manic again, he took me to the doctor. Three weeks of heavy sedation and lots of sleep brought me down, but then comes the depression. And so horrible is this hopelessness that I don't know how I survived it again. But today I feel good and I thank my God for restoring my mind to me today. It is my biggest prayer these days that my medication will work and keep me from getting sick again."

"My story and how I first developed this illness with these ephedra supplements will be in '*Self Magazine*' next month." This was back in April 2000. "And I'm a little nervous about seeing it. I hope it doesn't make me sound crazy."

It was in February 1996 that I first took these supplements containing ephedra and guarana. The ephedra was listed as "ma huang" on my bottle. That's the Chinese herbal name, and I just

[1] The prepared statement of Ms. Ruiz appears in the Appendix on page 118.

think that it's important to note that many of the dietary supplements out there do say ma huang. They don't say ephedra. But it's the same thing.

I had two small children and I was looking to lose post-pregnancy weight, also get a little extra energy. I was tired from getting up at night with the kids. I was drawn in by claims that it was all natural, and that it was safe. I had attended a meeting and asked questions about this product, and I was given brochures that used words like "doctor recommended," "scientific approach," and "quality assurance." I was very impressed with the entire presentation, and I found myself feeling very comfortable about taking these products. And I was pretty cautious. I didn't want to take anything that wasn't legal or drugs. I never had.

When I first started taking the products, I want to just tell you I immediately felt the lift in my energy. They said I would and I did. And for the first time in months, when my children took their naps, I didn't have to nap along with them. On day 3 after starting the product I woke up early and actually went to the gym before daybreak, and I came home and completely cleaned my house before the kids woke up.

My days were full and every minute was being used, and I felt very productive. There seemed to be no limit to my energy, and by day 4 I had come up with a new marketing plan for this company and was seeking legal advice on how to patent it. I had a lot of friends and a lot of moms who I knew needed this product. The energy was amazing.

But it was around day 5 that I began to feel something big was happening to me, and I still made no connection to the product. I was not getting as much sleep, and when I asked my direct distributor, and told him I was not getting as much sleep, his response was, "Isn't that great. You are getting so much healthier, you do not need as much sleep." That was not a red flag to him, it was not a warning, and if he was not concerned, I was not concerned.

I remember I was suddenly feeling very aware of a spiritual realm, and at one point I felt that I was being watched, and I remember thinking my neighbor was demonically possessed. I was flipping in and out of paranoia, but then followed by thoughts of what I presumed were divine and coming from God. I somehow was convinced that I was being chosen, initially to warn people that it was the end of the world. I went to my bank account, pulled out twenties and started handing them out to homeless people and saying, "We are almost there. We are going home."

Later, I thought I was being chosen to be God's wife, and eventually I just felt so euphoric and so in tune with the cosmic around us that I just thought I was God myself. It was an incredible way to feel, and I want you to know that I think I understand why people do drugs now. I had never experienced anything like that, and it does not surprise me to learn that teenagers and kids are using these products to get high. It is called herbal ecstacy on the streets.

By day 5 and 6, my husband knew something was wrong, and he took me to the hospital. They admitted me, and I was fortunate to have a psychiatrist who had been an emergency room physician prior to being here on this ward, and he took the supplements from

my husband. (My husband believed they were responsible.) The psychiatrist immediately identified the ephedra, the ma huang. There were some additional stimulants in the product, and he said, "She is on amphetamines. She is high."

I was there for 10 days, and after 10 days, a lot of medication, my mind did start to slow down, but I had a very hard time believing the things I was seeing, and hearing, and feelings were not real. I mean, I was seeing visions in the clouds. So, when you are seeing them, the person next to you cannot tell you that they are not there, because I was seeing them.

So I did eventually get well. It took 9 months, and following the initial incident—we did report it to the people who had sold it to me. Basically, they said, "Oh, gosh. We are really sorry. We have never seen that before. Bye." They never called or followed up or tried to get any kind of reaction. We felt lucky that we did have an attorney who knew me personally, knew that was very abnormal and had not happened to me before. He took our case on a contingency basis, and with lab tests, we realized that the products had no quality assurance. I had additional sources of ephedra in the product, in addition to the ma huang that was listed on the label. There were multiple kinds.

There was also guarana in the product not listed on the label, and I was taking it with another drink that was a guarana caffeinated drink so——

Senator DURBIN. Guarana is basically a stimulant?

Ms. RUIZ. Yes. The guarana is the herbal equivalent to caffeine, but there were no specifications of how much or anything like that. My cautions label said, "Don't take if you are a nursing or lactating mother or you are having high blood pressure," and that was about it, nothing else.

The doctors concluded that I had one of two things happen. I somehow had a predisposition toward mental illness which had never shown up before, and the supplements triggered its appearance or the supplements actually altered my natural brain activity and caused me to have symptoms similar to bipolar illness. Either conclusion is scary.

I know for a fact I am not alone. I have been fortunate enough to do some news clips and some media. It has been written up a few times, and I am amazed how many people actually see the article, make the connection of what is happening in their life, and they call me or it is the spouse of someone who calls me or it is a mother, and their daughter has been in the psychiatric hospital for 3 months, and she is just making the connection that she was taking Metabolife for 3 months before that.

And they are calling me looking for hope. They want to know what doctor I went to. They want to know how I got well, and they are lost. I always do my best to tell them how I got to a place where I could handle it and tell them to call the FDA.

So I would like to just conclude with my thoughts on what would have helped. Even those extensive labeling conditions would not have applied to me. I was completely healthy. I had no preexisting conditions, and so those warning labels did not apply to me.

I have seen them now in grocery stores. I did not use to see them so much, but now I can go to my coffee shop. They are all on the

counters. "Here, take this. Drink it with your coffee," you are out the door. They are everywhere.

Before I came, I walked into a Wal-Mart and bought three herbal products with no posted warnings anywhere. I would recommend posted warnings be required, at the very least. I also would recommend that number, the FDA's number, be put on all labels of these supplements immediately. We tried to report it to the FDA. We got lost in the phone loop, and I do not know if I am part of those statistics.

I would just like to conclude with saying that in articles I read, representatives for the industry repeated claim that cases like mine cannot be scientifically proven, and yet it is the industry which should have the requirement to prove that their products are scientifically safe. I did not abuse this product. I did not take more than was recommended. Until that can be done, and the medical communities agree, and the manufacturers, they both agree on some kind of safety standard, then I would like to see it pulled off the market.

So please use your influence and power to make a difference. Thank you.

Senator DURBIN. Thank you very much, Ms. Ruiz. Dr. Heymsfield, thank you for joining us.

Dr. HEYMSFIELD. Thank you very much.

Senator DURBIN. Your testimony will be part of the record, and we invite you to summarize it at this point.

**TESTIMONY OF STEVEN B. HEYMSFIELD, M.D.,[1] DEPUTY DIRECTOR, NEW YORK OBESITY RESEARCH CENTER, ST. LUKE'S-ROOSEVELT HOSPITAL CENTER, PROFESSOR OF MEDICINE, COLUMBIA UNIVERSITY, COLLEGE OF PHYSICIAN'S AND SURGEONS**

Dr. HEYMSFIELD. Thank you very much.

More than half of adult Americans suffer from overweight or obesity, and rates are skyrocketing in children and adolescents. Overweight and obesity are just spectrums of being overly fat.

Many of those who are overweight or obese suffer from related illnesses such as diabetes and cardiovascular diseases. The obese are discriminated against in all aspects of their lives—social, professional, and economic. Strong societal forces, along with the medical establishment, encourage overweight Americans to lose weight. A large percentage of overweight and obese individuals are currently dieting for weight loss at any point in time, as you had mentioned earlier.

While advances are rapid, almost breathtaking, scientists still do not have a complete fundamental understanding of why some people are prone to gain excess weight. Moreover, our nutritional medical treatments have limited effectiveness for the population as a whole. This creates a highly volatile combination: Tremendous consumer need and demand for weight-loss treatments, and yet a general lack of very effective nutritional and medical therapies. That is a very volatile combination.

[1] The prepared statement of Dr. Heymsfield with attachments appears in the Appendix on page 123.

The vulnerability of overweight and obese Americans to purchasing magic bullets or untested and unproven treatments has long been recognized by the FDA. The past is littered with unsafe weight-loss treatments ranging from nostrums in the 19th Century to amphetamines and Fen-Phen in the 20th Century.

Given the millions of Americans seeking weight-loss treatments, some of whom harbor silent and potentially lethal diseases, the FDA has set in place a rigorous system for two types of drug approval—prescription and over-the-counter, as we have already heard today. A critical issue is that drugs in either of these categories must not only be effective, but also be very safe so that benefits outweigh risks. Moreover, diet and exercise are always considered safe and inexpensive alternatives to pharmacologic treatments.

In 1994, as we know, a third category of weight-loss treatments emerged with the passage of DSHEA. An important concept inherent in the use of dietary supplements for weight loss is that beneficial effects would tend to be small, that is, less than that of a potent drug, and that by virtue of their presence in foods or herbs ingested by millions of humans over many, many centuries, they are inherently safe.

The very stringent safety and effectiveness standards set for weight-loss drugs by the FDA should, in theory, therefore, not need to apply to products marketed under DSHEA. Most overweight consumers view dietary supplements, as Ms. Ruiz told us, often consisting of herbs and other natural ingredients, as inherently safe.

As we will see shortly, this regulatory position opened the window for the marketing of ineffective and/or unsafe products to highly vulnerable populations. The available dietary supplements for weight loss purportedly suppress appetite, decrease hunger, limit nutrient absorption, alter the partitioning of fat and muscle or speed up metabolism.

Claims are that chitosan reduces fat absorption and promotes weight loss. Hydroxy citric acid, also known as garcina cambogia, blocks fat storage. Ma huang or ephedra suppresses appetite while speeding up metabolism, and chromium picolinate promotes muscle over fat formation.

Whether or not these dietary supplements work as proposed, to a large extent, remains uncertain. We lack adequate numbers or rigorous, mechanistic studies, and the benchmark for effectiveness, randomized, double-blind controlled trials.

To highlight the current concerns related to dietary supplements for weight loss, we can look at two groups of compounds, one that is inherently safe, but appears to be ineffective so far, and the other that is modestly effective, but appears to be inherently unsafe.

Garcinia cambogia, also known as hydroxy citric acid or HCA, is found widely in dietary supplements for weight loss and purportedly blocks the synthesis of body fat. However, our group, and no other scientist so far, have shown in well-designed clinical trials that HCA either promotes meaningful, long-term weight loss or reduces body fat beyond that of a placebo or dummy pill.

HCA has very minimal side effects, and the risk to consumers of ingesting these products appears to be negligible. The real risk is

to bypass a medical evaluation that might detect an underlying serious, and even life-threatening, medical condition.

The second example is based on the family of compounds that we have been discussing today that are extracted from plants referred to as ma huang or ephedra. Dietary supplements with ephedra are widely used by consumers for weight loss and to enhance athletic performance.

Ephedra alkaloids include ephedrine, the main ingredient in small amounts of pseudoephedrine, phenylpropanolamine, and other related molecules. Phenylpropanolamine or PPA was widely used in over-the-counter weight-loss products until recently when a commission study supported a significant link between hemorrhagic strokes and PPA.

As shown in the figure, which you can see up there, ephedrine and PPA bear strong structural similarities to amphetamines. Amphetamines were marketed for weight control beginning in the 1950's, but were addicting, had other serious medical side effects and were ultimately restricted by the FDA for weight-loss treatment. I should add, in the 1950's, I was told that there were very clean homes in the United States because amphetamines were strong stimulants, and we have heard from Ms. Ruiz, a very similar story about ephedra.

Most of the evidence we have so far is that ephedra alkaloids, notably ephedrine, act in the body in a manner nearly identical to that of the synthetic drug ephedrine. Dietary supplements with ephedra are usually sold in combination with an herbal source of caffeine. Caffeine, also a stimulant, amplifies the actions of ephedrine in the body.

The ephedra alkaloids and amphetamines are similar to the natural "fight and flight" hormone adrenaline. Like adrenalin, ephedrine speeds the heartbeat, increases blood pressure and stimulates respiration. These agents, their actions well understood at the molecular level, are termed sympathomimetics, and their actions center both in the brain and peripheral tissues.

Most of the high-quality research in this area was carried out using synthetic sources of ephedrine and caffeine in Europe, where the combination is usually used under medical supervision. Studies of dietary supplements with ma huang or ephedra are limited to short-term evaluations, usually less than 6 months. These studies, including some that I have participated in, reveal to us that ephedra with caffeine or dietary supplement counterparts produced a modest weight loss above that of placebo by roughly 2 pounds per month. These trials also reveal the expected stimulant effects of ephedra, palpitations, jitteriness and blood pressure elevations, to name a few. In our own study at the New York Obesity Research Center, an inordinate number of subjects dropped out of the protocol due to these stimulant side effects.

Although no heart attacks or strokes were reported in any of the previous controlled trials, we need to recognize that subjects are carefully screened. Those very individuals who harbor serious illnesses are usually eliminated from the study beforehand so as not to place them at risk. The subjects in these studies, thus, do not represent the consumer population. They are healthier.

Also, rare side effects would likely not be observed in the clinical trials that collectively to date have studied fewer than a thousand subjects.

While clinical trials confirmed the stimulant effects of ephedrine-caffeine combinations, the real safety concern comes from the untoward effects reported by individual consumers, like Ms. Ruiz, or their families to the FDA and from cases reported in the medical literature. While causality is hard to establish in many of these cases, we have strong evidence of an association between ephedra use for weight loss or physical activity enhancement and strokes, heart attacks and death.

Most of the individuals in these reported and analyzed cases were not taking excessive or inordinate amounts of product. These injuries are a predictable outcome of the known physiological actions of sympathomimetic agents such as ephedra alkaloids. These are not weakly effective agents to which humans have been exposed for thousands of years in the food supply.

As DSHEA now exists, the vulnerable, overweight and obese American public is exposed to an unfiltered and seemingly endless source of dietary supplements of questionable safety and effectiveness.

I implore you and other Federal officials to appropriately and ethically tighten this law.

Senator DURBIN. Thank you, Dr. Heymsfield.

As I mentioned at the outset of this hearing, there are a series of votes that are now underway, and I have a few minutes to get to the floor for the first of four. It could take 45 minutes before all of those votes are completed. I assure you I will return just as quickly as I can, but the hearing will stand in recess until the call of the Chair.

[Recess.]

Senator DURBIN. My apologies to everyone for the lengthy recess, but we had four votes, and on the Senate floor that can take some time.

I believe that the next witness is Mr. McGuffin. Please proceed.

**TESTIMONY OF MICHAEL McGUFFIN,[1] PRESIDENT, AMERICAN HERBAL PRODUCTS ASSOCIATION (AHPA), SILVER SPRING, MARYLAND**

Mr. MCGUFFIN. Thank you. Good, I guess it is afternoon now, and thank you for inviting me to testify here today. My name is Michael McGuffin, and I am President of the American Herbal Products Association or AHPA.

Prior to this hearing, this Subcommittee asked AHPA to provide responses to eight questions related to dietary supplements, and I do ask that AHPA's written responses be entered into the record.

Senator DURBIN. Without objection.

Mr. MCGRUFFIN. Six of the questions were directed to industry practices and self-regulation. AHPA has been actively involved in such efforts, and I want to describe two of them.

[1] The questions and answers included in the prepared statement of Mr. McGuffin from AHPA appears in the Appendix on page 139.

Many of our earliest self-regulatory efforts relate to herbs that must be used with caution. AHPA established several trade recommendations, and those also are in my written testimony. One example of these self-regulations is AHPA's policy on ephedra.

In 1994, AHPA established a label policy that ephedra products are not for use by children and that provides cautions for certain populations with preexisting conditions such as high blood pressure or diabetes. We revised this policy in 1995 to recommend dosage limits.

AHPA testified before FDA's Food Advisory Committee in both 1995 and 1996 and told them of our policies and urged them to recommend that FDA adopt them. In the meantime, the AHPA labeling has been adopted in several States.

In 1997, FDA proposed ephedra labeling and dosage limits, a proposal that was controversial and has, for the most part, been withdrawn. In May 1999, AHPA and other trade associations again recommended that AHPA's labeling and dosage guidance be adopted by FDA. This was repeated in October 2000 in the form of a citizen petition. There has been no action on the citizen petition, but the Department of Health and Human Services issued a statement last month regarding ephedra, and Mr. Levitt referred to that. The language that Mr. Levitt read very much models the industry labeling language as important information for consumers.

I want to give another example of AHPA's self-regulation that occurred in 1992, when we published a document called "Herbs of Commerce" to establish a single standardized common name for each of nearly 600 herbs. This was done to address potential consumer confusion because of the many different ways herbs are named.

In 1997, the Food and Drug Administration incorporated Herbs of Commerce into the Code of Federal Regulations so that the names established by AHPA now have the force of law. FDA's adoption of AHPA's Herbs of Commerce is an example of how government and consumers can benefit from industry's self-regulatory activities. The handling of the ephedra issue shows what can happen when positions become entrenched.

While there have been differences of opinion over the label language, these have been minor, and the principal controversies have been over dosage levels. Stepping back from the fray, I believe consumers would have been better served if FDA had promptly sought labeling while addressing dosage issues at a later date.

I want to address the common misperception that dietary supplements are unregulated. In fact the law requires dietary supplements to meet label claims, and these laws empower FDA to take enforcement action if a product fails to do so.

The law requires all dietary supplement labeling and advertising to be truthful and not misleading, and these laws provide FDA and the Federal Trade Commission with authority to enforce them.

The law places the responsibility for product safety squarely on the manufacturer, and it is a crime to introduce an adulterated product into the market.

AHPA believes that there is not enough FDA enforcement of the law and that the Agency's priorities are sometimes ill advised. When FDA does send warning letters, they are seldom followed up

with more aggressive enforcement when companies are not responsive. We have joined with other trade groups to successfully recommend an increase in FDA dietary supplement enforcement funding. I must say it is difficult for trade groups to urge members' compliance, when those members must confront unfair and unlawful competition on a day-to-day basis and not see FDA enforcing the law. It is time to see FDA take full responsibility for the implementation and enforcement of a law that is almost a decade old.

Let me close by saying that we are an industry that is committed to providing benefits to American consumers through our products, including products for those who are overweight at a time that the medical community has declared an epidemic of overweight in our country. "When Diets Turn Deadly" is a sensational title for today's hearing, and perhaps it evolves from recent history, not just in our industry, but also with drugs and problems in other countries.

The title is not, however, substantiated by any balanced, unbiased and thorough review of the body of science and experience for any of the dietary supplement agreements that are broadly available in the market, and that are manufactured, labeled and consumed according to established industry policies.

Thank you very much.

Senator DURBIN. Thank you, Mr. McGuffin. Ms. Culmo.

**TESTIMONY OF CYNTHIA T. CULMO, R.Ph.,[1] CHAIRPERSON, DRUGS, DEVICES, AND COSMETICS COMMITTEE, ASSOCIATION OF FOOD AND DRUG OFFICIALS, AUSTIN, TEXAS**

Ms. CULMO. Good afternoon. I am Cynthia Culmo. I am here as the chairperson for the Drugs, Devices and Cosmetics Committee with the Association of Food and Drug Officials. The points that I am making, as well as those in my written comments, are a compilation of comments that were submitted from multiple-State AFDO members. For the complete version of our position, please refer to those written comments.

We thank you, Mr. Chairman, for the opportunity to participate in this important and critical discussion. It is extremely difficult to roll in 8 years of experience, knowledge and information into 5 minutes, but for time's sake, I will try and summarize most of our concerning points.

There have been more serious adverse-event reports for dietary supplements containing ephedrine alkaloids than for any other type of dietary supplement or over-the-counter phenylpropanolamine drug products, which were recently withdrawn from all U.S. markets due to the increased risk of hemorrhagic stroke in young women.

These serious adverse-event reports included psychoses, seizures, strokes, heart attacks, and death. These are known and expected consequences on the use of ephedrine. Pharmacologically, as what has been discussed, in the body there is no difference between natural and synthetic ephedrine. They act the same in the body.

By regulation, drug products containing ephedrine cannot be combined with other stimulants. This is based upon the potential

[1] The prepared statement of Ms. Culmo with attachments appears in the Appendix on page 160.

for abuse and safety concerns. However, currently marketed dietary supplements for weight loss do contain ephedrine plus other stimulants.

Almost all of the products on the market are multi-ingredient products. They are ephedrine combined with other stimulants, diuretics, laxatives and other active ingredients. This explains the high number of adverse-event reports for these products.

You can see how well it is demonstrated—I believe the chart is up [1]—in the American Association of Poison Control Center data, as shown on this table, how the incidence of adverse-event reports has increased since the Dietary Supplement Health and Education Act.

These multi ingredients can interact with each other, with other products, being drugs and/or foods, and there are drug disease interactions. Studies are beginning to identify these complex interactions, which have definite effects on the safety of the products.

These products are also marketed for a disease—obesity. Although the industry routinely claims that their products are not drugs, they are posed to the consumer as drug products by their claims, the manner that they are advertised, as many of them are advertised in the Physician's Desk Reference for Nonprescription Drugs and Dietary Supplements now, as well as the way that the information is shared with health professionals and other consumer information, all of which results in misled consumers and medical professionals.

The studies that industry uses to support safety comes from foreign data on prescription drugs, using pharmaceutical ephedrine. None of these studies can be used to support the safety of dietary supplements. These products are not the same. There are numerous methodology problems with the relative few studies in the United States, which include, one, being too small; they are not using the marketed products. For instance, the industry-touted Boozer study, the 6-month study, it did not use Metabolife 356 as that company elaborates. So the results of these studies cannot be applied to the general population for weight loss.

DSHEA shifted the requirements proving a product is unsafe to the government. Many States have picked up this tremendous burden because of the apparent inability of the Federal Government to effectively address safety issues associated with these products.

The enforcement actions by the States are labor- and time-intensive. They are done with great difficulty and fierce battles with the industry and their political supporters. Politics and bureaucratic entanglements have prevented FDA and FTC from accomplishing their responsibilities.

Under DSHEA, safety is addressed after the harm has already occurred. The standards and the criteria of safety have never been defined by FDA or the courts. A major question that is yet to be answered is what is questionable or unreasonable risk that causes a product to be adulterated?

The most egregious safety problems with the dietary supplement for weight loss are the products containing ephedrine. The situation is not a scientific issue any longer. It is a political issue run

[1] The chart appears in the Appendix on page 173.

by a political agenda. There are ongoing conflicts between good public health and the industry's economic needs, with politics frequently serving as the referee.

Consumers are being misled, and they are not getting the full story about the risk associated with these products. They cannot make an informed decision about appropriate use. So labeling and warnings cannot solve safety issues. The warnings and the labels will not help when you do not know you have a condition that places you at increased risk.

This has been our most concerning point, and please refer to our written comments for a complete summary. But as you can see, the States have indicated that there are numerous problems associated with dietary supplements for weight loss, and they have recommended a number of solutions:

Except for traditional nutrients, such as vitamins, minerals, etc., prohibit or limit botanicals and other natural products to a single ingredient. I am sure that has made several in the room gasp, but this is exactly what Health Canada has done with ephedra. If you are going to retain a combination of products as a dietary supplement, then they should be required to have premarket review for safety;

Require manufacturers and distributors to register with the FDA and to list their products. This will enable FDA to develop appropriate product databases, to evaluate the product adverse-event reports, and the interactions;

Institute mandatory adverse-event reporting, which is analogous to what is required for drugs, biologics, and medical devices;

Implement a single adverse-event reporting system within FDA;

Adverse-event report evaluations and risk management is best directed by the regulatory agencies. Therefore, communications and interactions should be enhanced between State and Federal agencies and the general public;

Define the criteria for the DSHEA standard of significant or unreasonable risk. What is the standard to prove a product is unsafe? From a science perspective, if what is currently known about ephedra supplements cannot meet the standard, nothing else ever will;

Create a specific center within FDA for traditional medicines and dietary supplements for the regulatory oversight;

And last, and certainly not least, appropriate funding is necessary for all of the above.

In conclusion, we appreciate this opportunity to provide you with our comments. AFDO believes that products current marketed as dietary supplements for weight-loss purposes are either not safe or are of unknown safety, and the public health is not being adequately protected. Thank you very much.

Senator DURBIN. Thank you very much, Ms. Culmo.

Mrs. Ruiz, have you encountered individuals who continued to use these weight-loss supplements even though they told you they had had some bad side effects?

Ms. RUIZ. Actually, yes, and the reason for that is because they do not attribute the supplements to the problem.

I have been in contact with one family and he was training as an athlete. He was taking a product he bought at a bicycle shop.

And when he had heart palpitations, (he was running), they took him to the hospital. They told him he was low on electrolytes, so he went home and took more of the product to help with his electrolytes. He then had a full-blown psychosis after that.

So usually they do, but because they do not know it is causing the problem.

Senator DURBIN. Can you tell me how many individuals you estimate you have spoken to who have had negative experiences with ephedra-based dietary supplements?

Ms. RUIZ. Over the last 6 years, I have probably spoken with 10 very serious cases, and then quite a few individuals on a daily basis. I spoke at one recovery group with about 100 individuals in the room, and they were recovering from all kinds of things. I was talking about bipolar specifically, but I had talked about what triggered the event. After that meeting, I had six or seven different individuals come up to me who were dealing with depression, dealing with psychosis issues, and they were like, "I was taking this product and this product. And does this have ephedra in it?"

And all of them I was like, "Yep, yep, yep." I was amazed.

And then when I go to talk with my psychiatrist. (I have to see him for regular check-ups.) He explains how now he always asks more questions of new patients. Instead of just, "Are you on any prescriptions or illegal substances," now he goes beyond, and he says, "Are you taking any supplements, any vitamins? Have you been doing anything new lately?" And what he usually uncovers is that there is this supplement they have started. They think they are taking a vitamin but he has them bring them in. His cupboards are packed with Xenadrine and Metabolife, and Pure Ephedrene from GNC. And he is amazed how many people come in to see him.

So it is a daily thing for me to run into people like this.

Senator DURBIN. Dr. Heymsfield, have you had any patients in your practice who have had problems with dietary supplements?

Dr. HEYMSFIELD. Well, I have, particularly in the studies that we have done. When people go through the protocols, we have found that a number of them get side effects—jitteriness, headaches, palpitations, elevations in blood pressure. And when we take them off the study and break the code, we find that invariably they are on the active treatment which are ephedra alkaloids.

Senator DURBIN. We talked a little bit, Ms. Culmo spoke a little bit about combinations, and it appears that, unlike many products, some of these dietary supplements and herbal products have a range of different drugs in botanical form that are combined into these supplements. What kind of challenge does this create?

Dr. HEYMSFIELD. Well, it creates a number of challenges. First, those combinations usually amplify one another, so the effects can be fairly potent. Also, in the case of caffeine, many people continue to ingest caffeine in their daily lives out of colas, coffee, teas, and so on. So they can get a very high dose of caffeine. That amplifies the actions of ephedra alkaloids.

But the real challenge is we do not know how to assess the safety and efficacy of these combinations because they are so variable. One product might have a lot of one component and less of another, so it is virtually impossible to make global statements about the ef-

ficacy and safety of products as a whole because they are so variable in these combinations.

Senator DURBIN. As Ms. Culmo said, whether it is synthetic or botanical, it is still the drug that is being ingested into your system with the drug's impact.

Dr. HEYMSFIELD. Your body does not really know the source of where that molecule came from. It sees ephedrine, as either a botanical or a synthetic component, is identical.

Senator DURBIN. I guess it bears repeating that under the law we treat that entirely differently.

Dr. HEYMSFIELD. That is right.

Senator DURBIN. Whether you are dealing with a synthetic that is being prescribed or over-the-counter, it is subject to strict regulation in terms of how it is manufactured, how it is marketed, the quality of the drug, the dosage, the warnings, they are extensive. On the supplement side, there is very little, if any, regulation, in terms of those elements as I see them.

Now I would like to address the issue that Mr. McGuffin has raised. He has taken issue with my reference to the fact that the title of this hearing is "When Diets Turn Deadly." That was based on the Canadian situation where, in fact, they warned the people of Canada of possible fatal effects of these ephedrine dietary supplements, and so the title was chosen based on the experience of Canada.

Do you have any knowledge or any impression of this Canadian decision relative to these products, Dr. Heymsfield?

Dr. HEYMSFIELD. Do I have an opinion?

Senator DURBIN. Any knowledge or impression of this Canadian decision.

Dr. HEYMSFIELD. No, I do not, but it seems very well-founded, in my personal opinion, and it would seem, based on the same literature that I have reviewed, in the United States there have been a number of studies in very prominent journals showing the very high risk of ephedra alkaloids and ephedrine.

Senator DURBIN. The Canadians came to the conclusion that these products pose a significant threat of danger to the public health of their citizens. Do you believe that these products for sale in the United States pose a significant threat of danger to public health?

Dr. HEYMSFIELD. I do, and I will tell you why I feel that way, and that is because many of the people who take these products are just like Mrs. Ruiz, who do not really read the labels carefully, who harbor silent diseases, and that can be triggered by ingestion of these products. So I think it poses a very significant risk to people.

Senator DURBIN. Before asking Mr. McGuffin, I am going to ask the same question of Ms. Culmo. Do you feel, as a registered pharmacist, that these ephedra-based dietary supplements pose a significant threat of danger to the health of American citizens?

Ms. CULMO. Yes, definitely, and I believe the association would support the position as well. We are of the opinion that the evidence is there. The data and the information is available, and it is a conclusion that has been made by our association several times.

We would also venture to say that your title, "When Diets Turn Deadly," is appropriate, as I am sure that the families of the 100-plus people that allegedly died due to the association of these products supports the position that Canada took as well.

Senator DURBIN. Mr. McGuffin, I am not going to back off the title of this hearing. I think, based on what you have just heard from witnesses sitting on either side of you, and based on the decision of Canada, based on the letter you sent to the American Medical Association and the Food and Drug Administration, this is not a casual or minor problem. It is life-threatening in many instances.

Mrs. Ruiz was lucky enough to survive the situation. Thank goodness you are here today, and raising your family, and doing well. Hers was a terrible episode, but she survived it.

You have talked to me about industry standards. These are voluntary standards, are they not, within your industry?

Mr. MCGUFFIN. They are today. We have asked that they become the law.

Senator DURBIN. And those companies which market these products and do not belong to your association or do not subscribe to these standards may ignore completely the dosage requirements, the warning labels, the marketing, trying to keep these out of the hands of children; is that not true?

Mr. MCGUFFIN. It is true. We believe we have had an influence beyond our membership, but you know we have seen examples here today of products that would not conform with the labeling recommendations of our trade.

Senator DURBIN. Well, it strikes me that we are in a situation which is very strange, where your industry is coming forward and saying to the government, "Regulate us more. We want more regulation."

Mr. MCGUFFIN. Enforce these regulations.

Senator DURBIN. I think that is certainly overdue—8 years overdue. But before we reach that question of how we properly regulate these products so they are available, we have to ask, and answer, the threshold question, are they safe, and if they are not safe, there is no amount of regulation that could really cure the problem.

I guess that is a question I would ask, let us start with Dr. Heymsfield. In terms of dosage, there seems to be a wide variance of opinion here. The Canadians limit it to 32 milligrams a day. We hear 100 milligrams a day from many people in the dietary supplement industry.

You have done some studies on this subject. What can you tell me about dosage levels?

Dr. HEYMSFIELD. Well, the dosage levels that we used in our studies were those that are commonly used in these products as a whole, and certainly at those levels I would not say that we could assert these products are safe. The question of whether or not they might be safer at lower doses would have to be studied, and I have questions about that for the following reason, and that is if you lower the dose far enough, then you reduce the efficacy, the weight-loss efficacy, to the point where it would hardly be worth taking it. So I have questions about whether or not a dose reduction would totally solve the problem.

Senator DURBIN. So, if I were asking you to establish, based on a reasonable degree of medical certainty, as they say, a safe dosing regimen for a dietary supplement that still would provide the benefit of suppressed appetite, increased energy, are you saying that you would have a tough time finding that number?

Dr. HEYMSFIELD. A very hard time finding that number because when you got down to the levels I am hearing, the numbers I am hearing, you would get virtually negligible weight loss. The weight loss effects of ephedra alkaloids are already only two pounds a month at the current dosage, which I think is unsafe. If you, say, cut the dose in half or a third, you would almost wonder why you would want to take the drug, which is what I will call it.

Senator DURBIN. This is obviously a question which Secretary Thompson and the FDA has to resolve, whether on a public benefit basis, the risk that you are encountering is worth the benefit. If you can lose a pound a month or two pounds a month—is that based on some study, incidently, that two pounds a month that you have come with?

Dr. HEYMSFIELD. Well, there are growing numbers of collective analyses called, meta-alyses, that are looking at the efficacy of ephedra products, and the trend that I am seeing, including the studies we have done at our center, are in the range of about two pounds a month, and that varies a little. If you add the caffeine, you get a bit more.

Senator DURBIN. Of course, according to the Canadian standard, adding a stimulant or an analgesic, I think there has been some evidence that adding aspirin or some other form of analgesic could also create some complications with ephedra.

Dr. HEYMSFIELD. That is correct.

Senator DURBIN. Mr. McGuffin, you said that what you are looking for is a balanced, unbiased, and thorough review. Do you feel that Canada made a balanced, unbiased, and thorough review of dietary supplements that contain ephedrine?

Mr. MCGUFFIN. No, I do not, because my understanding is that the Canadian rule was based on the FDA proposal, which was based on Adverse Event Reports, and as the GAO has told us, they do not believe that that is a good way to get to a dosage recommendation.

I am concerned. If I can, I would like to repeat something that Mr. Levitt said earlier. He said that there is not a consensus on the meaning of the adverse event data that is as clear as you have described, sir; that it is not a black-and-white that we know that there is—that these adverse events point out a danger, and I think that it is important to remember that, and I am concerned that some of the information is not included.

If I may, I would like to ask that two other documents be entered into the record.[1]

Senator DURBIN. Without objection, certainly, it will be.

Mr. MCGUFFIN. There is a report called the "Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra" that was prepared for the Council for Responsible Nutrition by Cantox

[1] The information submitted by Mr. McGuffin appear in the Appendix on pages 146 and 157 respectively.

Health Sciences International and published in December 2000, that came to a conclusion that a dosage of 25 milligrams per serving and 90 milligrams per day is safe when used in accordance with standard industry labeling.

And there is a compilation of documents, comments of the expert panel of the Ephedra Education Council on the Safety of Dietary Supplements Containing Ephedrine Alkaloids, and it goes on for another two lines. This was presented in April 2000 at the hearing at the Office of Women's Health.

I think it is that document or these documents that Mr. Levitt was referring to, when we do not have a clear consensus. I appreciate greatly what these two scientists to either side of me are saying, and I do not believe any of us say that their points of view are crazy or unfounded, but there is not a consensus. There are other scientists who look at the same data and come to remarkably different conclusions by a very sophisticated scientific process, and that needs to be considered.

Senator DURBIN. I will readily concede that there are areas of science that are not precise. Certainly, political science is not precise. [Laughter.]

Mr. MCGUFFIN. Did you win all four votes? [Laughter.]

Senator DURBIN. But I can tell you this, I have spent a career on this Hill listening to the scientific analyses of the tobacco companies. They always found a doctor, they always found a scientist who could just prove to you that it could not possibly cause heart disease, and cancer, and stroke and all of the rest.

And so I think what we have to do is ask what is a reasonable scientific basis acknowledged by most, if not all, to base our conclusions.

I am troubled by the adverse event reporting that we heard of earlier. To think how few, some estimate that only 1 percent of the adverse events relating to dietary supplements ever reach the FDA, and you heard the examples of the Poison Control Centers. Ms. Culmo made that point as well. In 1 year they had 13,000 reported events, and in that same year, fewer than 500 were reported to the FDA.

That suggests to me, Mr. McGuffin, that you cannot really get into the circular argument of the FDA that we would really like to establish standards, but we need more adverse events reported to do that. We do not have enough adverse events reported, and therefore there will be no standards. Meanwhile, we seem to be, as we stand here, watching group after group, State after State, organization after organization, and now countries saying the United States is completely out of control here.

Mr. MCGUFFIN. Again, we have assisted many of those States in adopting our policy. You pointed out 21 States. I was not aware of that many, but we worked hard in several States to assist a process that would put our recommended labeling and dosage limit in place and make it the law in those States. We are very supportive of that.

Senator DURBIN. Was that part of your effort recently in Texas?

Mr. MCGUFFIN. We were involved in the communication with Texas. We were concerned, at least an initial stage, on the inclusion of the 800 number because we think that system needs to be

patched up some. There are problems with the system, but we were involved in that, and their warning label is very similar to the one that we have been using for some years.

Senator DURBIN. You have all been very patient, but I want to conclude the hearing, if I can, by asking an open-ended question.

It strikes me that we have two extremes here in terms of Federal regulation. We have the regulation of drugs, which clearly involves extensive testing and determination of safety and efficacy before it can ever be sold in the United States. Then it is sold only with a doctor's supervision, by his prescription, her prescription, and of course dosage and everything is being carefully monitored.

Circulars are sent to the doctors, to the pharmacy with all sorts of information. Ms. Culmo, I bet you are called on from time-to-time by patients who say, "Look at all of these medicines I am taking. Do they work together?" That is part of the people in pharmacology.

So we have a very thorough system of regulation, approval and monitoring when it comes to drugs.

Then, when we get into the supplements and food area, it is totally the opposite, where you have a situation where the company that makes the product decides what to put in it, the manufacturing practices to follow, in terms of making certain that it is unadulterated and is what it says on the label, the representations on the label have to stand some tests, at least by the Federal Trade Commission, maybe by the FDA. Ultimately, the whole question of dosage and warning labels is still voluntary. The adverse event reporting, still completely voluntary on the part of the manufacturer. So we have this wide chasm between these two approaches.

It strikes me that most people would concede that when it comes to basic things like Vitamin C, and folic acid, that this supplement in food approach is not to be quarreled with. I mean, we are talking about something that is fundamentally safe. You would have to have hyper dosages to have very bad results. But now we have got a middle category. We have a middle category of supplements that are combinations of naturally occurring chemicals that are life-threatening, in some instances, and certainly can create terrible medical situations. I think Congress has defined the extremes, and now has to come to the center.

I would like to ask you, Dr. Heymsfield, do we need to come up with a new regimen of regulation for supplements, let us start with dietary supplements, that perhaps does not go as far as drugs, but takes us forward in terms of protecting American consumers?

Dr. HEYMSFIELD. Well, for one thing, we might consider changing the name. Dietary supplement certainly gives the impression that it is something normally in the diet or that it is supplementing something normally in the diet. If products are specifically, say, for body building, and they are anabolic steroid derivatives or if they are for weight loss and they are ephedra alkaloids, we might want to name them a little more specifically so consumers really understand what they are getting.

I also feel strongly that these regulations should be tightened and that we should have much clearer guidelines for safety and efficacy of these products, and we should seek experts out like Na-

tional Academy of Sciences and other esteemed bodies that can help us with these.

Senator DURBIN. Ms. Culmo, what is your feeling about establishing some new category of regulation?

Ms. CULMO. Well, I believe that was part of our position through our comments. I think it is also evidence from what other countries do. The industry here is pretty quick to point out that these are dietary supplements that have been used for thousands of years in other countries, are currently used in other countries, when the truth of the matter is they are actually addressed more commonly as prescription drugs or prescription products in these countries, and the traditional use is very different from what the commercialized use is right now.

So, definitely, it needs to be changed.

Senator DURBIN. Mr. McGuffin, what is your reaction?

Mr. MCGUFFIN. I would be very troubled by the idea of creating a new regulatory category as much as anything because, as you have pointed out, it is 8 years in, and we have not figured out how to properly implement this one.

You have heard my testimony. What we believe needs to occur is that the current law needs to be enforced. There may be some refinements that would be appropriate for discussion. But the idea of just wholesale starting a new category, just off the top of my head here, sir, with no consultation with any of my Members, concerns me.

Senator DURBIN. I would say to you that you can argue that if the current law were properly funded and enforced, we might not be facing the problems we are today. The fact is that the government has not met its obligation and, as Ms. Culmo has suggested, there has been extraordinary political involvement in terms of decisionmaking when it comes to dietary supplements. That is a fact of political life.

I have been around here 20 years. The reaction to this hearing on Capitol Hill, and off Capitol Hill, has been stronger than virtually any issue I have raised, including my hearings on tobacco. So I know that there are a lot of strongly held views by consumers, as well as the representatives of the industry in this town.

But I honestly believe that we have to come up with a better answer. I do not think what we have today is adequate. The first thing that we have to do is establish whether these products are safe, and if they are not safe, then, frankly, that is the end of the story, as far as I am concerned.

I am going to be calling on the Department of Health and Human Services and the Food and Drug Administration to make a timely determination whether the continued sale of dietary supplements containing ephedra create an imminent hazard to public health in our Nation, and if such a determination is made, whether the sale of these products should be restricted or regulated to protect consumers.

I am also going to work on legislation to develop a commission for a scientific study to conclusively address the question of the safety of dietary supplements. I believe, as well, that we need to establish an effective mechanism for banning the sale of dietary supplemental products, particularly ephedra and ephedrine-con-

taining supplements to minors. We should draw this line and draw it clearly.

I want to work as well with consumers, industry and Federal agencies to establish a mandatory—mandatory—Adverse Event Reporting System that will effectively inform the FDA, consumers, companies and health care professionals when dangerous products have been identified.

I believe we should modify the current definition of dietary supplement categories so as to highlight the difference between vitamins and minerals, potent herbal products that act like drugs, and animal derivatives, as well as exclude steroid precursors, like andro, from the dietary supplement category.

I am going to press the FDA for the immediate release of good manufacturing practices and pursue with the Federal Trade Commission ways to further their efforts to eliminate deceptive supplement marketing claims.

I would like to close this hearing by thanking this panel for your cooperation and your patience as I went off to vote. I want to particularly thank my staff that has been involved in this, Dr. Melanie Leitner, a congressional science policy fellow, who has worked harder on this than anybody on my staff. Thank you, Melanie, for all you have done.

Anne Marie Murphy, Brian McLaughlin, Tom Faletti, Emily Kirk, Joe Shoemaker, Maria Domanskis, Marianne Upton, and a team of intrepid interns, thank you all very much for this hearing.

[Whereupon, at 1:18 p.m., the Subcommittee was adjourned.]

# APPENDIX

## PREPARED OPENING STATEMENT OF SENATOR VOINOVICH

Good morning, and thank you Mr. Chairman for holding this hearing on this topic which directly impacts the lives of millions of Americans.

While Governor of Ohio, I signed the first law in the Nation establishing a balanced and fair approach to the sale of ephedra. Since then, other States have passed similar laws, including Hawaii, Michigan, Nebraska, and Washington. In 2000 California passed a similar law, but Governor Grey Davis vetoed the measure because he believed that the Federal Government should set the standard.

It is my understanding that although the FDA is required by a 1994 law to issue Good Manufacturing Practice (GMP) standards for the supplements industry; the agency has yet to finalize these standards. Let me repeat that, 8 years after Congress passed the law, the FDA has not issued the regulations. This is an action the agency can and must take.

Responsible members of this industry have actively sought appropriate, science-based regulation to ensure that consumers are well educated through factual labeling and that dietary supplements are manufactured in a consistent and quality manner. Additionally, industry has agreed to a ban on the sale of ephedra products to minors. Unfortunately, not all players in the market are responsible. It is these bad players that bring us here today.

In our oversight role, we need to ensure that Americans are able to count on existing regulatory agencies to protect and promote their well-being. I hope the work being done by the National Institutes of Health, even as this hearing takes place, will help us to understand just where we need to go on this important issue.

Thank you, Mr. Chairman.

United States General Accounting Office

GAO

Testimony

Before the Subcommittee on Oversight of Government Management, Restructuring, and the District of Columbia, Committee on Governmental Affairs, U.S. Senate

For Release on Delivery
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# DIETARY SUPPLEMENTS FOR WEIGHT LOSS

## Limited Federal Oversight Has Focused More on Marketing than on Safety

Statement of Janet Heinrich
Director, Health Care—Public Health Issues


GAO-02-985T

Mr. Chairman and Members of the Subcommittee:

I am pleased to have the opportunity to testify as the Subcommittee considers concerns about dietary supplements that are used for weight loss.[1] Since the enactment of the Dietary Supplement Health and Education Act (DSHEA) in 1994, U.S. sales of weight loss supplements have increased steadily. The sales revenue of weight loss supplements—reported to be the fastest growing segment of the dietary supplement industry—increased 10 to 20 percent annually from 1997 to 2001, and industry officials expect that rate of increase to continue. The prevalence of obesity has increased in the United States, and many Americans are looking for ways to help them lose weight. It is estimated that Americans spent almost $2 billion on weight loss supplements in 2001. As sales of weight loss supplements have increased, so have concerns associated with their marketing and use. Regulators, medical experts, and the dietary supplement industry recognize that some weight loss supplements may be marketed with overstated claims, such as "lose weight while you sleep." In addition, some weight loss supplements have been reported to be associated with serious side effects for some people.

Various government agencies have a responsibility for oversight, research, and education efforts related to weight loss supplements. The Federal Trade Commission (FTC) and the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) have oversight responsibility for products marketed as weight loss supplements. Marketing includes both advertising activities and product labeling. FDA oversees the manufacture and labeling of weight loss supplements, but is not required by DSHEA to approve dietary supplements for safety or efficacy. FTC is responsible for ensuring that the advertising for these products is not unfair or deceptive. HHS's National Institutes of Health (NIH) funds research to determine the safety and efficacy[2] of weight loss supplements. All three agencies carry out some consumer education activities. State agencies also enforce individual states' laws that govern the sales and marketing of particular supplements.

[1]Generally, when we refer to weight loss supplements, we are referring to individual ingredients, not specific products or brands, some of which might contain multiple ingredients. Weight loss supplements include herbal or other botanical ingredients such as aloe, ephedra, fiber, and green tea; minerals such as chromium and pyruvate; as well as amino acids, enzymes, and tissues from organs or glands.

[2]Efficacy is the ability of a substance to produce the intended effect under ideal conditions of use.

Because of the concerns surrounding the marketing and use of weight loss supplements, you asked us to examine these issues and how they are being addressed by federal and state agencies and the dietary supplement industry, as well as in the courts. My remarks today will focus on (1) safety and efficacy concerns associated with weight loss supplements; (2) federal oversight, research, and public education efforts; and (3) state and local regulatory efforts aimed at consumer protection, including litigation concerning weight loss supplements.

In our examination of these issues, we reviewed scientific literature about weight loss supplements, as well as federal and state regulatory activities involving weight loss supplements. In addition, we interviewed and obtained documents from officials at FDA, FTC, and NIH. We also interviewed representatives of trade associations and interest groups pertinent to dietary supplements and weight loss. We identified dietary supplements commonly used or marketed for weight loss and possible side effects or contraindications for those supplements (see the appendix for a list of these supplements).[3] However, our work does not represent an exhaustive review of the efficacy or safety of particular weight loss supplements, nor did we look at meal replacements, over-the-counter drugs, or prescription medications. We provided a draft of this testimony to FTC, FDA, and NIH for their review. In oral comments, the Director of FDA's Center for Food Safety and Applied Nutrition agreed with our statement. FTC and NIH declined to provide official comments. FTC, FDA, and NIH provided technical comments which we have incorporated where appropriate. We conducted our work from May through July 2002 in accordance with generally accepted government auditing standards.

In summary, little is known about whether weight loss supplements are effective, but some supplements have been associated with the potential for physical harm. Health consequences, which can be serious, may result from the use of the supplement itself or from the interaction of the supplement with medications or foods. People with certain underlying health conditions, such as heart disease, high blood pressure, and diabetes, may be particularly at risk. In addition, supplements may be contaminated with harmful ingredients or may not contain the amount of an active ingredient that is stated on the label. Federal and state activities

[3]Although we did not focus on supplements that are marketed exclusively as performance enhancement supplements, some supplements with weight loss claims also make performance enhancement claims.

related to weight loss supplements have been limited and have focused on oversight of marketing more than on oversight of safety. FTC has prosecuted manufacturers of weight loss supplements for making misleading claims. FDA has issued warnings for some products and ingredients. However, FDA faces difficulty in addressing safety concerns due in part to weaknesses in its adverse event reporting system. The agency must also meet different standards for addressing safety concerns with supplements than it uses for drugs. Further, FDA has been slow to issue good manufacturing practice (GMP) regulations. Federal agencies have also been involved in research and education. NIH's National Center on Complementary and Alternative Medicine (NCCAM) has determined that weight loss supplements are not as high a priority as its other areas of research. Both FTC and FDA have developed publications and Internet sites on weight loss that provide some educational materials to consumers. In addition, several states have statutes or regulations in effect or pending to restrict the sale of some weight loss supplements. Some state attorneys general and local district attorneys have sued the manufacturers of supplements marketed with weight loss claims, and individuals have sued over injuries.

## Background

More than half of U.S. adults are overweight or obese, and more than one-third of U.S. adults are trying to lose weight.[4] Increasingly, they are turning to weight loss supplements for help. The most widely used weight loss supplement is ephedra, or *ma huang*. The active ingredients in ephedra—ephedrine alkaloids—are compounds with potentially powerful stimulant effects on the nervous and cardiovascular systems. The dietary supplement industry estimates that as many as 3 billion servings of ephedra are sold each year in the United States and approximately 12 million individuals were using ephedra in 1999.

FDA regulates dietary supplements under DSHEA, which covers vitamins, minerals, herbs or other botanicals, amino acids, certain dietary substances, or derivatives of these items. A product that contains any active ingredient not on the preceding list—such as synthetic ingredients that are sold in over-the-counter drugs and prescription medications—may not be marketed as a dietary supplement. DSHEA requires that dietary supplement labels include complete lists of ingredients and the amount of

[4]A.H. Mokdad and others, "The Continuing Epidemics of Obesity and Diabetes in the United States," *Journal of the American Medical Association*, vol. 286 (2001), pp. 1195-1200.

each ingredient in the product. Products may be labeled as "proprietary blends" and must list all ingredients but do not need to list the amount of each ingredient. In addition, dietary supplements cannot be promoted as a treatment, prevention, or cure for a specific disease or condition. To the extent that therapeutic claims are made, FDA may take action.

FDA generally oversees the safety of dietary supplements. It may issue a regulation, for example, to prevent the further marketing of dietary supplements that it has determined pose an unreasonable risk of illness under the recommended conditions of use. A dietary supplement may also be removed from the market if HHS finds that it poses an imminent hazard to public health and safety. However, under DSHEA, it is the manufacturer who is responsible for ensuring the safety of the weight loss supplements it sells. Dietary supplements do not need approval from FDA before they are marketed. DSHEA does not require manufacturers to register with FDA,[5] identify the products they manufacture, or provide reports of adverse events—harmful effects or illnesses—to FDA. However, FDA is authorized to issue regulations governing GMPs to standardize manufacturing, packaging, and holding practices.

Since manufacturers of dietary supplements are not required to provide reports of adverse events to FDA, the agency and others rely on voluntary postmarketing reporting of adverse events to better understand the safety of dietary supplements. In addition to these adverse event reports, FDA uses data from poison control centers, reports and inquiries from consumers and health care providers, and complaints from trade competitors to track potentially dangerous supplements. These reporting systems can then be used to signal safety concerns. There are numerous problems with this passive system of adverse event reporting, and these have been noted extensively in our earlier work.[6] For example, only a small proportion of adverse events are reported, and those reports often are incomplete or contain inconsistent information.

[5]Under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Publ. L. No. 107-188, manufacturers and distributors of dietary supplements will now be required to register with FDA no later than Dec. 13, 2003.

[6]U.S. General Accounting Office, *Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids*, GAO/HEHS/GGD-99-90 (Washington, D.C.: July 2, 1999), and *Health Products for Seniors: "Anti-Aging" Products Pose Potential for Physical and Economic Harm*, GAO-01-1129 (Washington, D.C.: Sept. 7, 2001).

In an effort to control unfair or deceptive acts or practices in the marketplace, FTC oversees dietary supplement advertising to ensure that product claims are truthful and substantiated. Manufacturers and distributors of weight loss supplements make a wide variety of claims about how their products work. They claim that the supplements reduce appetite or cravings, increase metabolic rate, have a laxative effect, and block digestion of fat, carbohydrates, sugars, or starches. Manufacturers frequently combine multiple supplements into single products, promoting several pathways to weight loss. FTC can demand that false, exaggerated, or unsubstantiated claims be removed from advertising, and it also can seek monetary relief for injurious conduct. The marketing of unsafe products or potentially dangerous products without adequate safety warnings could violate the Federal Trade Commission Act.

Federal research regarding the safety and efficacy of weight loss supplements marketed to the public is carried out under NIH sponsorship. The agency's NCCAM is primarily responsible for federal research on complementary and alternative medicine, including dietary supplements, although other NIH institutes may also fund such research. Generally, NCCAM funds clinical trials to evaluate the safety and efficacy of popular alternative medicine products and therapies of interest. NIH's Office of Dietary Supplements (ODS) supports research and disseminates research results in the area of dietary supplements. Specifically, ODS plans, organizes, and supports conferences, workshops, and symposia. Although ODS can initiate such activities, it generally works in conjunction with other NIH institutes and centers and other groups.

States and individuals can also take action against manufacturers of weight loss supplements. States can enact and enforce laws and regulations to protect consumers from dangerous weight loss supplements and false or misleading advertising. Individuals can file lawsuits against manufacturers alleging injury from using weight loss supplements.

## Little Evidence of Efficacy Exists for Weight Loss Supplements, and Some May Have Serious Health Consequences for Certain Individuals

There is little evidence on whether weight loss supplements are efficacious. However, we identified several ways that weight loss supplements might cause health risks. Many weight loss supplements have been associated with side effects, some of which can be serious. Some weight loss supplements should be avoided by individuals with certain medical conditions because particular effects of the supplements could exacerbate the conditions. In addition, some weight loss supplements have potentially dangerous interactions with prescription or over-the-counter medications or foods. Further, a supplement may contain dangerous contaminants or different amounts of an active ingredient than indicated on the product label. Finally, we found multiple-ingredient products to be of particular concern because of the increased difficulty involved in evaluating and understanding their safety.

### Little Evidence Exists on Efficacy of Weight Loss Supplements

For most weight loss supplements, little scientific evidence to date supports their efficacy. Although there have been studies on specific ingredients, many of these studies have been of short duration, involved small numbers of individuals, or used study approaches that limited the usefulness of their findings. There have been few comprehensive reviews or long-term studies of efficacy. One comprehensive review of alternative treatments for weight loss found no reliable scientific evidence for the efficacy of any of the weight loss supplements that it reviewed.[7] Another review found similar results except for ephedra.[8] Most of the research that has been done to evaluate the efficacy of weight loss supplements has involved ephedra. A recently published randomized study found that a combination of ephedra and kola nut (a source of caffeine) promoted

[7]G. Eggar and others, "The Effectiveness of Popular, Non-prescription Weight Loss Supplements," *Medical Journal of Australia*, vol. 171 (1999), pp. 604-8. This study examined bladderwrack (*Fucus vesiculosus*), brindle berry (*Garcinia cambogia*), caffeine/guarna, capsaicin, chitosan, chromium picolinate, ginkgo biloba, grapeseed extract, horse chestnut (escin), L-carnitine, lecithin, pectin, St. John's wort, and sweet clover/soybeans (isoflavones).

[8]D.B. Allison and others, "Alternative Treatments for Weight Loss: A Critical Review," *Critical Reviews in Food Sciences and Nutrition*, vol. 41 (2001), pp. 1-28. The authors reviewed bladderwrack (*Fucus vesiculosus*), brindle berry (*Garcinia cambogia*), chitosan, chromium, conjugated linoleic acid (CLA), dehydroepiandrosterone (DHEA), ephedra, germander, ß-hydroxy-ß-methylbutyrate (HMB), plantain/psyllium, pyruvate, St. John's wort, and sunflower.

weight reduction.[9] Other smaller studies have shown similar results for ephedra.[10]

## Adverse Effects, Contraindications, and Interactions Are Associated with Weight Loss Supplements

Available research on weight loss supplements, though limited, in general suggests that some supplements are associated with both minor and potentially serious adverse effects. Further, many supplements are contraindicated for individuals with some underlying health problems. That is, there are specific dangerous side effects for persons with certain health conditions. In addition, a variety of weight loss supplements can have dangerous interactions with prescription and over-the-counter drugs that are being taken concurrently. However, just as with research on efficacy, few systematic studies exist on the negative health consequences of particular weight loss supplements. Adverse effects, contraindications, and interactions that have been associated with some of the more commonly used weight loss supplements are shown in the appendix.

The side effects associated with weight loss supplements are generally mild and may include unpleasant digestive symptoms, insomnia, or rash. However, for some supplements there may be more serious adverse effects. For example, dehydroepiandrosterone (DHEA) may increase the risk of some hormone-related cancers. Both aloe taken internally, such as in a dieter's tea, and chromium may also increase the risk of cancer. FDA has identified illnesses and injuries reported to be associated with the use of selected weight loss supplements, including yohimbe, which has been associated with renal failure, seizures, and death, and ephedra, which has been associated with seizures, heart attacks, psychosis, stroke, and death.

Use of some weight loss supplements has been found to be contraindicated, or inadvisable, for persons with certain preexisting medical conditions. For example, bitter orange (*Citrus aurantium*) should be avoided by persons with certain heart conditions. DHEA may worsen prostate hyperplasia.[11] Neither herbal laxatives found in dieter's

[9]C.N. Boozer and others, "Herbal Ephedra/Caffeine for Weight Loss: A 6-Month Randomized Safety and Efficacy Trial," *International Journal of Obesity*, vol. 26 (2002), pp. 593-604. This study focused on otherwise healthy adults who were overweight or obese, and excluded from review persons with insulin-controlled diabetes, high blood pressure, active heart disease, or other illnesses.

[10]F. Greenway, "The Safety and Efficacy of Pharmaceutical and Herbal Caffeine and Ephedrine Use as a Weight Loss Agent," *Obesity Reviews*, vol. 2 (2001), pp. 199-211.

[11]Benign prostatic hyperplasia is the abnormal growth of benign prostate cells.

teas nor fiber should be used by persons with intestinal obstructions. Fiber and gymnema may affect persons with diabetes. These risks are of particular concern because serious health conditions, such as hypertension and diabetes, often go undiagnosed.[12] Consumers who have undiagnosed medical conditions and inadvertently use contraindicated dietary supplements may expose themselves to considerable risk.

Using weight loss supplements along with certain prescription medications and certain foods poses an additional risk. For example, fiber may alter the effects of some medications. Other supplements, such as DHEA, may duplicate the effects of prescription medications. Similarly, aloe and chromium affect blood sugar levels and may require altering the dosage of medication for diabetes. And many supplements, such as fiber, green tea, and guggul, may alter the effects of anticoagulant medications. Yohimbe and St. John's wort should not be used with certain foods (such as red wine, liver, and cheese) because they may cause a toxic reaction, and chitosan may affect the absorption of certain vitamins. The possibility of such interactions is of particular concern because it has been reported that more than 18 percent of those who use a prescription drug also use a dietary supplement, and further, about 60 percent of people who use dietary supplements do not discuss their supplement use with their doctors.[13]

## Product Contamination and Content Variation May Pose Health Risks

Contaminated supplements and those with different amounts of active ingredients than indicated on the labels, or different active ingredients altogether, can pose significant health risks to consumers. Research has found supplements contaminated with pesticides or heavy metals, some which are probable carcinogens and are toxic to the liver and kidneys. O commercial laboratory found contamination in samples of the weight los supplements St. John's wort and chromium. For dietary supplements in general, the same laboratory found that 24 percent of the 62 herbal products it tested, particularly those containing ginseng, and 4 percent of

[12]It has been estimated that more than one-third of those with hypertension or high blood pressure and up to one-half of those with diabetes are unaware of their condition.

[13]D.M. Eisenberg and others, "Trends in Alternative Medicine Use in the United States, 1990-1997," *Journal of the American Medical Association*, vol. 280, no. 18 (1998), pp. 1569-75; and D.W. Kaufman and others, "Recent Patterns of Medication Use in the Ambulatory Adult Population of the United States," *Journal of the American Medical Association*, vol. 287, no. 3 (2002), pp. 337-344.

the 68 nonvitamin, nonmineral supplement products it tested were contaminated in some way.

Amounts of active ingredients can vary from what is indicated on a product label. Too much of an active ingredient may increase the risk of overdose for some consumers. Studies of DHEA, ephedra, and St. John's wort found that a number of products have substantially more active ingredient than indicated on the label. One brand of DHEA was found to contain 150 percent of the amount of active ingredient indicated. A study of ephedra showed that one product contained as much as 154 percent of the amount indicated. Too little of an ingredient can also pose a risk. For example, one chromium product tested by a commercial laboratory had less than 5 percent of its claimed amount of chromium. Because chromium can affect insulin and blood sugar levels, diabetics taking products containing chromium may attempt to adjust their medication dosage to compensate. However, if the chromium product does not contain the stated amount of active ingredient, the consumer may over- or undercorrect his or her dosage.

Further, products may contain active ingredients not on the label. In 2002, the International Olympic Committee (IOC) found that of 634 nutritional products tested, 15 percent contained ingredients banned by the IOC but not listed on product labels. Of the countries whose products were tested, the United States had the most products—19 percent—that contained ingredients that had been banned and were not listed on product labels.

## Multiple-Ingredient Products Pose an Unknown Risk

Of particular concern to some federal officials is the widespread prevalence of multiple-ingredient weight loss supplements. Rarely do weight loss supplements contain just one active ingredient. In fact, multiple-ingredient products account for 85 percent of the weight loss supplement market. We found products containing as many as 22 active ingredients, all of which are classified as dietary supplements. In considering the scientific literature relevant to weight loss supplements, we found that although the majority of products marketed for weight loss contained more than one active ingredient, the majority of the research and evidence of adverse events is reported for each individual ingredient, not for multiple-ingredient products. FDA officials reported that there is little systematic research on individual ingredients and virtually none on multiple-ingredient products, with the possible exception of ephedra with caffeine. With multiple-ingredient products, potentially dangerous interactions may be more likely, as has been suggested with the combination of ephedra and caffeine, both stimulants.

It is more difficult to study the safety and efficacy of multiple-ingredient products because each product may have a different combination of ingredients, meaning that each individual product would need to be studied. Further, the amounts of ingredients in a product may be unknown if the product contains a "proprietary blend" of various ingredients. Proprietary blends must list ingredients but are not required to specify the amount of any individual ingredient. Finally, it is harder to identify patterns in the adverse events associated with multiple-ingredient products and attribute the events to either an individual ingredient or a combination of ingredients. A study found that in 95 percent of the adverse events reported to FDA for products containing chromium, the products also contained as many as 11 additional ingredients, any of which may have been responsible for the adverse event. It is also possible that it is the interaction of these ingredients that is responsible for the adverse events.

## Limited Federal Efforts Have Focused More on Oversight of Advertising and Labeling than on Oversight of Safety

Federal oversight, research, and education efforts to protect and inform consumers about the potential risks associated with the use of some weight loss supplements have been limited. They have focused almost entirely on marketing issues such as advertising and labeling, rather than on safety issues associated with particular weight loss supplement ingredients. These efforts include carrying out enforcement activities against companies, funding research to evaluate weight loss supplements, and providing educational materials on potentially dangerous ingredients and fraudulent product claims. Since 1995, FTC, which generally oversees the advertising of weight loss supplements, has taken 30 actions related to supplements. FDA, which regulates the manufacturing and labeling of weight loss supplements, has taken 16 actions against manufacturers in the same period. FDA has faced difficulty in addressing safety concerns and has been slow to issue GMPs for dietary supplements. Although federal agencies have not given priority to research on weight loss supplements, they do provide some educational material to consumers.

### FTC Has Focused Its Oversight and Enforcement Efforts on Advertising

FTC staff told us that the agency has taken legal action in 30 cases involving the advertising of weight loss supplements since 1995, after DSHEA went into effect. These actions resulted in more than $21.5 million in monetary relief and consumer redress. In addition, as of June 2002, FTC staff reported that they had a significant number of investigations pending against different manufacturers of weight loss supplements. In 2000, Enforma Natural Products agreed to a settlement with FTC regarding deceptive claims for two products and agreed to pay $10 million in consumer redress. The products, a chitosan-based product called "Fat

Trapper" and a pyruvate product named "Exercise In A Bottle" made claims such as

- "you can eat what you want and never, ever, ever have to diet again,"
- "you can enjoy all these delicious foods like fried chicken, pizza, cheeseburgers, even butter and sour cream, and stop worrying about the weight," and
- "foods you can eat when you crave them without guilt, without worry, and it's all because of a few little capsules."

However, in 2002, the company was still marketing the products in question. Since the filing of the final judgment in that case, FTC attorneys have filed two contempt actions against Enforma to enforce the provisions of the court's order. In 1999, FTC action was upheld in a case against SlimAmerica for its "Super-Formula," consisting of three different pills, containing chromium picolinate, hydroxycitrate (HCA), chitin, and konjac glucomannan (a soluble fiber).[14] The company was ordered to pay more than $8.3 million in consumer redress. In addition, the president and vice president of the company were ordered to post a $5 million and a $1 million performance bond, respectively, prior to engaging in any business related to weight loss products or services.

To help manufacturers better understand the advertising restrictions and requirements for dietary supplements, FTC issued a guide for advertising dietary supplements in November 1998. In addition, FTC conducts outreach to the industry regarding responsible advertising.

## FDA Has Focused Its Oversight and Enforcement Efforts on Labeling

FDA is involved in varied activities to protect consumers of weight loss supplements, including enforcement actions against manufacturers for improper labeling and publication of a proposed rule regarding ephedra dosing. FDA has taken 16 enforcement actions since 1995 against the manufacturers of dietary supplements marketed with weight loss claims, and the majority of these have been for products that are improperly labeled as dietary supplements. For example, FDA determined in 1999 that Triax Metabolic Accelerator, labeled as a dietary supplement, was an unapproved new drug that contained a potent thyroid hormone that could cause heart attacks and strokes. The manufacturer agreed to stop

[14]These products claimed they would "'blast' up to 49 pounds off in only days, 'obliterate' five inches from waistlines, and 'zap' three inches from thighs—all without the need to diet or exercise."

distributing products containing the specified ingredient. In 2001, FDA took action resulting in the seizure of $2.8 million worth of AMP II Pro Drops, an unapproved drug product that contained ephedrine from a nonherbal source but was labeled as a dietary supplement. The manufacturer agreed in 2002 that it would not manufacture and distribute such products in violation of the law. In June 2002, FDA sent six more warning letters to companies that were also marketing nonherbal ephedrine products as dietary supplements.

In fiscal year 2002, FDA has allocated $1.4 million to support enforcement initiatives against manufacturers of dietary supplements making unsubstantiated labeling claims. From February 1997 through January 2002, FDA issued seven warning letters to manufacturers of weight loss products, focusing mainly on the labeling of these products. Five of these warnings were for products labeled as alternatives to the prescription drugs fenfluramine and/or phentermine, also known as Fen-Phen. These actions were taken because labels for dietary supplements cannot contain references to prescription drugs.

The only enforcement action FDA has taken on the basis of safety concerns specific to weight loss supplement ingredients came in 2001, when the agency warned consumers not to use LipoKinetix because of multiple reports of liver injury or failure while using the product. This product contained, among other things, caffeine and yohimbe. In addition, the agency issued a letter to health care professionals and the distributors of the product alerting them to the product's risks and asking distributors to voluntarily remove the product from the market.

To date, the most concerted attempt taken by FDA to protect consumers of weight loss supplements has been its effort to regulate dietary supplements containing ephedra. In 1997, FDA published a proposed rule regarding the dosing and labeling of products containing ephedra. After public comment and following our report on the subject that was critical of the science FDA used to develop some of its proposed rule,[15] the agency withdrew the parts of the proposed rule on dosing; the remaining elements focus on warnings and combinations with other ingredients. In June 2002, the Secretary of Health and Human Services announced that HHS was funding a comprehensive review of the existing science on ephedrine

[15]GAO/HEHS/GGD-99-90.

alkaloids as input to the proposed rule. This study is supported through the Agency for Healthcare Research and Quality.

## FDA Has Faced Difficulty in Addressing Safety Concerns

FDA has been hindered in its ability to address safety concerns with weight loss supplements by weaknesses in its adverse event reporting system. Further, its authority to address potential safety concerns for weight loss supplements is different from that for drugs.

Weaknesses in the adverse event reporting system include difficulty in detecting patterns of events, as well as in obtaining voluntary adverse event reports. Adverse event reports are often incomplete and contain inconsistent information. Officials reported that it is easier to identify patterns with over-the-counter drugs and pharmaceuticals than with dietary supplements because there is a better understanding of the biological mechanisms of action from preclinical testing of these drug products and because manufacturers of such products that have approved applications are required to report adverse events to FDA. In contrast, it can be difficult to detect patterns for serious adverse events for dietary supplements in part because of the absence of preclinical testing. Nevertheless, HHS has reported that a pattern of potentially related events has been identified from adverse event reports for products containing ephedra, although questions remain on the strength of the products' association to the adverse events reported to FDA. The voluntary, or passive, nature of the adverse event reporting process for dietary supplements contributes to the difficulty in establishing causal connections. One manufacturer received more than 1,200 complaints of adverse events for a weight loss supplement containing ephedra, but, because there is no reporting requirement for dietary supplements, it did not forward any of these reports to FDA. The HHS Inspector General reviewed the adverse event reporting system in April 2001.[16] In response to that review, FDA is developing a new reporting system with an emphasis on dietary supplements, which should be available in mid-2003. Agency officials stated that the new system will enhance FDA's ability to capture data and follow up on event reports, but reporting will remain voluntary.

Although agency officials stated that the criteria they use to review adverse events reported for dietary supplements and for over-the-counter

[16]HHS, Office of Inspector General, *Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve*, OEI-01-00-00180 (Washington, D.C.: April 2001).

or prescription drugs are the same, the authority to regulate dietary supplements, and to take action on safety concerns, is different from that for drugs. When FDA has health concerns about an over-the-counter ingredient, or combination of ingredients, the agency may determine that it is not generally recognized as safe and effective, and may issue a regulation or take other action to prohibit further marketing. FDA is not required to find that an over-the-counter drug is unsafe or dangerous to remove it from the market. In the case of dietary supplements, more significant safety concerns would have to be identified. For example, FDA is authorized to take regulatory action against a dietary supplement if its use would present a significant or unreasonable risk of illness under recommended conditions of use. If FDA were to take such action, however, it must be prepared to prove its allegations either in an administrative hearing or court. Unlike its regulation of over-the-counter drugs, FDA has the burden of proving that a dietary supplement presents a significant or unreasonable risk before it can be taken off the market.

These differences in regulatory standards are reflected in differences in actions taken for similar or identical ingredients. Specifically, FDA has concluded that two categories of products are not generally recognized as safe and effective and cannot be marketed for over-the-counter use. These categories of products, however, may be used in dietary supplements. First, in September 2001, FDA ruled that over-the-counter drugs containing ephedrine and related alkaloids in combination with an analgesic or stimulant would be removed from the list of ingredients generally recognized as safe and effective, and thus could no longer be marketed as drugs. There is no similar rule prohibiting the manufacture and marketing of dietary supplements containing herbal ephedra in combination with herbal analgesics or stimulants. Second, in May 2002, the agency issued a rule that the stimulant laxative ingredients aloe and cascara sagrada in over-the-counter drugs are not generally recognized as safe and effective and cannot be marketed. However, these ingredients may be marketed in dietary supplements and are commonly found in dieter's teas.

## FDA Has Been Slow to Finalize Good Manufacturing Practice Regulations

FDA has drafted GMP regulations for dietary supplements but has been slow to finalize these regulations. GMPs would standardize manufacturing, packaging, and holding practices for dietary supplements. The agency published an advance notice of proposed rule making for GMPs in February 1997. A draft proposed rule was developed during the summer of 2000. The new administration was given the opportunity to review the proposed rule, and HHS as well as the Office of Management and Budget had significant comments. Currently, the rule is in administrative

clearance with HHS. As we have previously stated,[17] publication of final GMP regulations will improve FDA's enforcement capabilities, since DSHEA provides that dietary supplements not manufactured under conditions that meet GMPs would be considered adulterated.[18] FDA would be able to take enforcement action against the manufacturers of adulterated products if they were subject to GMP regulations.

Meanwhile, four private efforts are under way to review the manufacturing practices of supplement makers and evaluate the ingredients in dietary supplement products. Specifically, the U.S. Pharmacopeia, Good Housekeeping Institute, consumerlab.com, and NSF International each have voluntary programs in which manufacturers submit products and pay a fee to get their products reviewed. These programs do not look at product safety, but rather focus on label accuracy. In addition, the National Nutritional Foods Association, a trade association representing manufacturers of dietary supplements, has two programs to help ensure product quality.[19]

## Weight Loss Supplements Have Not Been a Federal Research Priority

NIH officials reported that research on weight loss supplements is not a priority and the agency has not made any formal program announcements or requests for proposals to study weight loss supplements. However, the agency has sponsored limited research on weight loss supplements through two of its research institutes and centers. In fiscal year 2001, NCCAM spent $627,000 of its annual budget of $89.1 million on research of weight loss supplements.[20] The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) currently supports investigator-initiated research on conjugated linoleic acid (CLA) and chromium picolinate.[21] In addition, NIH has supported other research on ingredients found in weight

[17]GAO-01-1129.

[18]Generally, adulteration refers to products that may contain contaminants or are otherwise unsafe.

[19]The GMP certification program for the association's members uses third-party inspectors to ensure that products meet their purported quality and entitles the manufacturers to use the association's GMP certification mark. The quality assurance program provides for random, independent tests of products.

[20]NCCAM studied ephedra and caffeine, the mechanics of ephedra, and the insulin regulation properties of ginkgo biloba.

[21]These studies were funded for a total of $228,710 in fiscal year 2001 by ODS and the Office of the Director.

loss supplements, though not in studies specifically related to weight loss. Data from this research may help address the safety of some of these supplements. Further, the National Institute of Environmental Health Sciences and the HHS National Toxicology Program are conducting toxicological research on weight loss supplements in animals to further understand their potential adverse effects in humans.

ODS officials reported that the office had been asked by the Congress to work with other federal agencies to study the safety and efficacy of dietary supplements in general and develop a research agenda on the safety and efficacy of ephedra, specifically. It is starting with a systematic evidence-based review of ephedra. This review is funded by ODS and NCCAM through the Agency for Healthcare Research and Quality's Evidence-based Practice Program, and the findings are scheduled for release in the fall of 2002.[22] ODS is also working with other agencies and trade associations to develop analytic tools and standards for testing supplements. In addition, the National Heart, Lung, and Blood Institute is working with ODS to offer a workshop on weight loss supplements to review scientific evidence and identify research gaps.

FDA has funded the Institute of Medicine's Food and Nutrition Board to develop a "Framework for Evaluating the Safety of Dietary Supplements" that will allow the agency to prioritize further research on dietary supplements, including weight loss supplements, by identifying which ingredients are of the greatest concern. The framework will also establish a methodology for doing rigorous safety evaluations. A preliminary framework is currently undergoing review, and the final report is expected to be available by the end of 2002.[23]

## Federal Agencies Provide Some Educational Materials to the Public

FTC and FDA have programs designed to provide the public with information about healthy weight loss practices, including weight loss supplements. FTC has Operation Waistline, which, among other activities, highlights fraudulent claims made by the manufacturers and distributors of weight loss products. FTC also has a number of links on its Web site encouraging consumers to beware of certain advertising claims that may

[22]This study, performed under contract with RAND, was supported with $380,000 from ODS and $100,000 from NCCAM.

[23]Institute of Medicine, "Proposed Framework for Evaluating the Safety of Dietary Supplements" (draft) (Washington, D.C.: National Academy Press, July 2002).

be associated with some weight loss products. In addition, in an effort to demonstrate to consumers how Web sites selling such products may be misleading, FTC has developed a Web site designed to look as if it is selling a real weight loss supplement. However, once a customer tries to make a purchase, the Web site informs the customer that he or she would have been scammed had this been a "real" Web site. According to agency officials, this Web site has been visited more than 9,000 times since 1998. In general, FDA makes information about supplements available to the public through its Web site and media announcements. Two publications, "Tips for the Savvy Supplement User" and "An FDA Guide to Dietary Supplements," together provide a general overview of the dietary supplement industry. FDA provides updated information with periodic news and warnings about specific products.

## State Consumer Protection Efforts Include Legislation and Litigation

Some states have adopted a variety of statutes and regulations to protect consumers from potentially dangerous supplement ingredients and fraudulent supplement marketing practices. In addition, there have been state and local lawsuits aimed at the manufacturers of some weight loss supplements over product claims and private lawsuits over injuries.

### State Statutes and Regulations

States have adopted statutes and regulations specific to the sale of certain weight loss supplements. Most of these states' actions control the sale of ephedra; the exception is California, which requires a warning label for products containing herbal ingredients with a laxative effect, such as senna, aloe, buckthorn, cascara, grangula, and rhubarb root. The majority regulate ephedra in connection with the regulation of controlled substances. Generally, ephedra is regulated to deter its use in the illegal manufacture of the controlled substance methamphetamine, rather than its use as a dietary supplement. Some states have prohibited ephedra sales to minors, some have declared it an illegal drug, and others have adopted regulations on how and to whom it can be sold[24] (see table 1).

[24]In addition, the National Football League, NCAA, IOC, and U.S. Olympic Committee ban the use of ephedra and its active ingredient, ephedrine.

Table 1: State Statutes or Regulations on Ephedra in Effect as of July 2002

| State | Ephedra in controlled substance statutes or regulations | Requirements | | | Comments |
|---|---|---|---|---|---|
| | | Dosing limits[a] | Warning label | Cannot sell to minors | |
| Arkansas | X[b] | | | | Regulation applies to all products containing ephedra as the sole active medicinal ingredient or in combination with therapeutically insignificant quantities of another active medicinal ingredient or ingredients. |
| Hawaii | X[c] | X | | | |
| Michigan | X[c] | X | X[d] | X | |
| Nebraska | | X | X[e] | | Previously, Nebraska had banned the sale of ephedra. |
| Ohio | X[c] | X | X[d] | X | |
| Oklahoma | X[c] | X | X[d] | | |
| South Dakota | X[b] | | | | Dietary supplements containing ephedrine or "ma juang" (sic) are controlled substances and cannot be sold legally without a prescription. |
| Texas | | | X[e] | X | |
| Virginia | | | | X | Any product combining caffeine and ephedrine sulfate cannot be sold to minors without a prescription. |
| Washington | | X | | | Use of ephedra requires a prescription if dosing limit requirements are not met. |

[a]Dosing generally limits serving size to 25 mg, for a total of not more than 100 mg per day.

[b]All products containing ephedra are considered controlled substances.

[c]Ephedra is exempted as a controlled substance providing certain requirements about dosing or warnings are met.

[d]Warnings state that improper use may be hazardous to one's health.

[e]Warnings generally suggest consulting a physician, using with caution for those with certain diseases, and discontinuing use if negative side effects are experienced.

Source: GAO analysis of state laws.

Texas has the most specific regulations for products containing ephedra concerning product content and labeling. In addition to the requirements stated in table 1, each batch of a product must be analyzed to ensure that it contains the amount of total ephedrine alkaloids listed on the product label. In addition, labels must include the amount of caffeine and other stimulants, cautions about use with caffeine, and FDA's toll-free telephone number for reporting adverse events.

Other states are considering legislation to regulate ephedra. For example, in May 2002, the California State Senate passed a bill that would ban the sale of ephedra to minors, require prominent warning labels, and include a toll-free telephone number to FDA so consumers can report adverse events. California also has proposed that school districts be required to provide students with information on the effects of and the dangers of ephedra. Massachusetts has proposed ephedra legislation that would limit dosing and require warning labels. Idaho's Board of Pharmacy has also proposed establishing labeling, content, and registration requirements for ephedra, as well as banning the sale to minors. Both New York and New Jersey have proposed legislation that would prohibit the sale of products containing ephedra to persons under age 18.

## State, Local, and Private Lawsuits

Some state attorneys general and local district attorneys have sued marketers or manufacturers of weight loss supplements over marketing claims. One California county district attorney told us that since the mid-1990s, his office has prosecuted more than 30 consumer protection cases involving weight loss products, all of which were settled, with penalties ranging from $5,000 to $500,000. For example, this county sued Enforma (as did FTC, see above) and received $500,000 in civil penalties and costs, including a $100,000 penalty against its celebrity spokesperson. The Pennsylvania Attorney General has also settled with two companies. In one case, a product claimed numerous health benefits such as that consumers could lose 17 pounds in 1 month and that the product "reduces fat and calories automatically by carrying them out of your body before they could be absorbed." The distributor is prohibited from selling or delivering the product in the state, and agreed to offer full refunds and pay $2,000 in civil penalties and $1,500 in investigation costs. In the second case, the company claimed the product would "flush calories right out of your body" and that consumers could "eat all you want and still lose weight." The manufacturer agreed to stop making unsubstantiated claims, add disclosures to its product labels, and pay $2,000 in civil penalties and $3,000 in investigation costs.

Attorneys involved in private lawsuits reported that most private lawsuits alleging injuries from weight loss supplements are settled out of court and do not go to trial. However, in 2001, a jury awarded $13.3 million to a woman who suffered a debilitating stroke after taking a dietary supplement containing ephedra for weight loss. This particular product also contained synthetic stimulants that are not considered dietary supplements, and the manufacturer had received warnings about the product from FDA.

## Conclusions

To date, federal activity on weight loss supplements has focused on oversight of marketing more than on oversight of safety. Federal activity has focused less on safety in part because FDA is largely dependent on voluntary reporting of adverse events for information on safety. It is also more difficult for FDA to identify patterns of safety concerns for dietary supplements than for drugs. FDA's authority to regulate dietary supplements is different from its authority to regulate drugs and it has a greater burden of proof to take action against supplements that may be unsafe. Because of these differences in regulatory authority, some weight loss products with similar or identical active ingredients may be marketed as dietary supplements, but not as drugs.

Further, research specific to weight loss supplements has not been a priority for federal agencies. There have been few systematic studies of weight loss supplements. Consequently, little is known about whether weight loss supplements are effective, but many of them have been reported to be associated with the potential for physical harm. However, as the upward trend in sales and use is expected to continue, more consumers may be at risk of adverse events related to use of the supplements. Consumers need scientifically accurate information about safety and efficacy to help guide their choices about weight loss supplements.

Mr. Chairman, this completes my prepared statement. I would be happy to respond to any questions you or other Members of the Subcommittee may have at this time.

## Contact and Acknowledgments

For more information regarding this testimony, please call Janet Heinrich at (202) 512-7119. Key contributors include Marcia Crosse, Carolyn Feis Korman, Jennifer Cohen, Charles Davenport, Julian Klazkin, and Roseanne Price.

# Appendix: Identified Adverse Effects, Contraindications, and Interactions Associated with Weight Loss Supplements

We focused our review on dietary supplements that are commonly used for weight loss.[1] For each supplement, we have listed in table 2 the adverse effects that have been reported to be associated with the supplement, conditions for which the supplement might be contraindicated, and prescription medicines and foods with which the supplement might have dangerous interactions. The sources we used to generate this table gathered information from laboratory, animal, and human studies. The evidence from human studies includes case reports, observational studies, and clinical trials. We have not independently validated these associations.

**Table 2: Identified Adverse Effects, Contraindications, and Interactions Associated with Commonly Used Dietary Supplements Promoted for Weight Loss**

| Supplement | Identified adverse effects | Identified contraindications | Identified interactions |
|---|---|---|---|
| Bitter orange (*Citrus aurantium*) | Sensitivity to light and increased blood pressure. | Should be avoided by individuals with cardiovascular concerns such as hypertension. | |
| Bladderwrack (*Fucus vesiculosus*) | High doses and prolonged use associated with risk of iodine overdose and hyperthyroidism. | Should be avoided by individuals with hyperthyroidism. Long-term use is not recommended. | May have an additive effect with antihyperglycemic medications. |
| Brindle berry (*Garcinia cambogia*) (hydroxy citric acid) | High doses associated with gastrointestinal (GI) distress. | Should be avoided by individuals with diabetes and dementia syndromes. | |
| Caffeine (guarana, cola nut) | GI distress, nausea, dehydration, headaches, insomnia, nervousness, anxiety, muscle tension, heart palpitations, increased blood pressure, addiction, and possible genetic damage. | Should be avoided by individuals with gastric ulcers. High doses and long-term use are not recommended. | May strengthen the action of central nervous system stimulants that reverse depression. |
| Chromium | Mild GI distress, anemia, blood abnormalities, liver dysfunction, renal failure, memory loss, rhabdomyolysis, tissue damage, genetic damage, genetic mutation, and cancer. | Should be used with caution by individuals with a history of hypoglycemia. Should be used only under medical supervision by individuals with a history of hyperglycemia or type II diabetes. High doses of chromium picolinate are not recommended. | May cause corticosteroid-induced diabetes when taken with corticosteroid medications. |

[1]To be included in the table, a supplement had to be listed in at least two of the following sources as having a weight loss claim: supplementwatch.com; supplementinfo.com; *Nutrition Business Journal*, D.B. Allison and others, "Alternative Treatments for Weight Loss: A Critical Review," *Critical Reviews in Food Sciences and Nutrition*, vol. 41 (2001), pp. 1-28; and G. Eggar and others, "The Effectiveness of Popular, Non-prescription Weight Loss Supplements," *Medical Journal of Australia*, vol. 171 (1999), pp. 604-8.

**Appendix: Identified Adverse Effects, Contraindications, and Interactions Associated with Weight Loss Supplements**

| Supplement | Identified adverse effects | Identified contraindications | Identified interactions |
|---|---|---|---|
| Conjugated linoleic acid (CLA) | GI distress and nausea. | | Should not be used with medications, mineral oil, dietary supplements, or food additive s that prevent absorption of fats. |
| Dehydroepiandrosterone (DHEA) | Altered hormone profiles, increased facial hair, acne, scalp hair loss, oily skin, mood swings, aggressiveness, irritability, virilization in women and gynecomastia in men, a deepening of the voice, and menstrual cycle irregularities. Also associated with insomnia; headaches; nervousness; fatigue; low energy; decreased high density lipoprotein (HDL) cholesterol ("good cholesterol"); cardiac arrhythmias; liver abnormalities; hepatitis; and increased risk of heart disease, diabetes, stroke, and some hormone-related cancers. | Should be used only under medical supervision by individuals at risk for hormone-related cancer such as prostate, ovarian, endometrial, and breast cancer. Long-term use may worsen prostate hyperplasia. High doses are not recommended. | May alter the effects of antidepressants, estrogen and estrogen-like medications, anticoagulants, central nervous system stimulants, and diabetic/hypoglycemic medications. |
| Dieter's teas (containing aloe, buckthorn, cascara, castor oil, rhubarb root, senna, or other herbal laxatives) | GI distress, stomach cramps, pain, constipation, nausea, vomiting, and diarrhea (sometimes chronic), fainting, dehydration, electrolyte disorders, potassium deficiency, nephropathies, edema, accelerated bone deterioration, and cardiac arrhythmias. Aloe taken orally may increase risk of cancer. | Should be avoided by individuals with abdominal pain of unknown origin, diarrhea, dehydration, intestinal obstruction, and any inflammatory condition of the intestines (appendicitis, colitis, Crohn's disease, irritable bowel syndrome, or ulcerative colitis). Aloe should be avoided by individuals with hemorrhoids or kidney dysfunction. Rhubarb should be used with caution by individuals with a history of kidney stones. Use for more than 2 weeks is not recommended. | May alter the effects of antiarrhythmics, digoxin, digitalis, electrolytes, nonsteroidal anti-inflammatory drugs, and decrease the absorption of other oral medications. Potassium deficiencies associated with use of stimulant laxatives can lead to disorders of heart function and muscle weakness, especially with concurrent use of cardiac glycosides, diuretics, and corticosteroids. Aloe may lower blood sugar levels and alter the effect of diabetic/hypoglycemic medications. Senna decreases the absorption of estrogens. |
| Ephedra (*ma huang*) | Loss of appetite, nausea, vomiting, disturbances of urination, sweating, pupil dilation, insomnia, irritability, nervousness, dizziness, shortness of breath, elevated body temperature, tremor, muscle injury, nerve damage, severe headaches, memory loss, psychosis, increased blood pressure, heart palpitations, seizures, stroke, heart attack, and death. High doses associated with dependency. | Should be avoided by individuals with glaucoma, thyroid disease, diabetes, high blood pressure, or heart disease. Should also be avoided by individuals with difficulty in urination due to prostate enlargement. Should be used only under medical supervision by individuals with a kidney disorder, psychiatric disorder, or seizure disorder. Should discontinue use at least 24 hours prior to surgery. | May alter the effects of cardiac medications. Should not be used with other medications, including nonprescription allergy, asthma, cold/cough, weight control products, and antidepressants. Use of ephedra with monoamine oxidase (MAO) inhibitors strengthens the stimulant action of ephedra and may result in life-threatening fever, hypertension, and coma. |

**Appendix: Identified Adverse Effects, Contraindications, and Interactions Associated with Weight Loss Supplements**

| Supplement | Identified adverse effects | Identified contraindications | Identified interactions |
|---|---|---|---|
| Fiber (chitosan, psyllium, methylcellulose, glucomannan, pectin, or others) | GI distress including gas; bloating; intestinal cramps; abdominal distention; nausea; diarrhea; choking; and obstruction of the esophagus, throat, and intestines. | Should be avoided by individuals with a history of intestinal obstruction, fecal impaction, or narrowing of the gastrointestinal tract, and those who have difficulty controlling their diabetes. Should be used with caution by individuals with shellfish allergies and insulin-dependent diabetes (insulin and/or medication levels may need to be adjusted). | May alter the effects and decrease the absorption of diabetic/hypoglycemic medications, cholesterol-lowering medications, anticoagulants, digoxin, and other oral medications. High intake may decrease absorption of fat-soluble vitamins (A, D, E, and K) and carotenoids (such as beta-carotene, lutein, and zeaxanthin). |
| Green tea (catechins) | GI distress, decreased appetite, insomnia, nervousness, hyperactivity, increased blood pressure, increased heart rate, and gastric irritation. High doses associated with headache, heart palpitations, and vertigo. | Should be used with caution by individuals with renal disease, hyperthyroidism, susceptibility to spasm, anxiety, and panic disorder. Should be used only under medical supervision by individuals with peptic ulcers, cardiovascular disease, and blood clotting abnormalities. High doses should be avoided by individuals with irregular heartbeat. Should discontinue use at least 24 hours prior to surgery. | May alter the effects of anticoagulant medications and supplements (including vitamin E and ginkgo biloba), resulting in decreased platelet aggregation (blood clotting) and increased bleeding times. |
| Guggul (myrrh) | GI distress, diarrhea, nausea, and skin rash. | Should be used only under medical supervision by individuals with hyperthyroidism. | May alter the effects of thyroid medications, cholesterol-lowering medications, anticoagulants, antiplatelet medications, propranolol, and diltiazem. |
| Gymnema | GI distress. Extremely high doses associated with hypoglycemia. | Should be used only under medical supervision by individuals with active diabetes. | May alter the effects of oral hypoglycemics and insulin. Antidepressants, including St. John's wort and salicylates (white willow and aspirin), may enhance the effects of gymnema. Stimulants, including ephedra, may reduce its effectiveness. |
| HMB (ß-hydroxy-ß-methylbutyrate) | | | |
| 5-Hydroxytryptophan (5-HTP) | Nausea, vomiting, diarrhea, loss of appetite, difficult breathing, pupil dilation, blurred vision, abnormally sensitive reflexes, loss of muscle coordination, and cardiac arrhythmias. | Should be avoided by individuals with any significant cardiovascular disease. Should be used only under medical supervision by individuals with cancerous tumors. | Should not be used with MAO inhibitors, other antidepressants (including herbal remedies such as St. John's wort), or prescription weight loss medications. |
| L-Carnitine | Nausea, vomiting, diarrhea, abdominal cramps, and seizures. | Should be used only under medical supervision by individuals with thyroid disease or seizure disorder. | |

**Appendix: Identified Adverse Effects, Contraindications, and Interactions Associated with Weight Loss Supplements**

| Supplement | Identified adverse effects | Identified contraindications | Identified interactions |
|---|---|---|---|
| Pyruvate | GI distress including nausea, gas, bloating, and diarrhea. | Should be used only under medical supervision by individuals with blood clotting abnormalities. Should discontinue use at least 14 days prior to surgery. | |
| St. John's wort | GI distress, nausea, loss of appetite, constipation, dry mouth, sensitivity to light, allergic reactions, skin rash, hives, tiredness, fatigue, insomnia, restlessness, dizziness, confusion, and fast or irregular breathing. | Should be avoided by individuals who are attempting to become pregnant (may be mutagenic and toxic to sperm), and individuals who have received organ transplants or are taking medications that decrease immune system activity. Should be used only under medical supervision by individuals with severe depression. | May alter the effects of oral contraceptives, decrease the effectiveness of HIV medications, immunosuppressants, digoxin, anticoagulants, chemotherapy, and asthma medications. May alter the effects of other prescription or over-the-counter medications. Should be used only under medical supervision when taking MAO inhibitors or other prescription antidepressants. Should not be used with tyramine-containing foods (certain wines, liver, and cheeses). |
| Vanadium | GI distress. High doses and long-term use associated with muscle cramps, depression, and damage to the nervous system and other organs. | Should be avoided by individuals with hyperglycemia, hypoglycemia, or diabetes. | |
| Yohimbe | Queasiness, vomiting, insomnia, headache, sweating, flushing, nervousness, tension, tremors, difficulty breathing, hallucinations, anxiety, psychotic episodes, increased blood pressure, increased heart rate, heart palpitations, and chest pain. High doses associated with decreased blood pressure, GI distress, and unpleasant central nervous system symptoms. | Should be avoided by individuals with low blood pressure, diabetes, high blood pressure, kidney disease, liver disease, chronic inflammation of the sexual organs or prostate gland, cardiovascular disease, women who could become pregnant, and elderly persons. High doses and long-term use are not recommended. | Should not be used with antidepressant medications or supplements, nasal decongestants, weight loss supplements with ephedrine, or tyramine-containing foods (certain wines, liver, and cheeses). May increase the effect of MAO inhibitors and hypotensive drugs. May alter the effects of psychopharmacological herbs. |

Note: We do not include any adverse effects or contraindications specific to infants, children, pregnant women, or nursing mothers.

Sources: *Physicians' Desk Reference for Herbal Medicines*, 2nd ed. (Montvale, N.J.: Medical Economics Company, Inc., 2000); *Physicians' Desk Reference for Nutritional Supplements* (Montvale, N.J.: Medical Economics Company, Inc., 2001); M. Blumental, ed., *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines* (Boston, Mass.: American Botanical Council, 1998); K. Bruss, ed., *American Cancer Society's Guide to Complementary and Alternative Cancer Methods* (Atlanta, Ga.: American Cancer Society, 2000); M. McGuffin and others, eds., *American Herbal Products Association's Botanical Safety Handbook* (Boca Raton, Fla.: CRC Press LLC, 1997); and D.B. Allison and others, "Alternative Treatments for Weight Loss: A Critical Review," *Critical Reviews in Food Sciences and Nutrition*, vol. 41 (2001), pp. 1-28. See also www.fda.gov/fdac, www.supplementwatch.com, and www.supplementinfo.org.

# Testimony

**Before the Subcommittee on Oversight of Government Management, Restructuring and the District of Columbia**

**Senate Governmental Affairs Committee**

**U.S. Senate**

## "When Diets Turn Deadly: Consumer Safety and Weight Loss Supplements"

## Testimony of Michael F. Mangano

**Principal Deputy Inspector General**

July 31, 2002
10:00 a.m.
342 Dirksen Senate Office Building

**Office of Inspector General**
**Department of Health and Human Services**
**Janet Rehnquist, Inspector General**

**Testimony of**
**Michael F. Mangano, Principal Deputy Inspector General**
**Department of Health and Human Services**

INTRODUCTION

Good morning Mr. Chairman and Members of the Subcommittee. I am Michael Mangano, Principal Deputy Inspector General for the Department of Health and Human Services. I appreciate the opportunity to be part of today's hearing on consumer safety and weight-loss supplements and to share with you the results of our work on the effectiveness of the Food and Drug Administration's (FDA) adverse event reporting system for dietary supplements. Millions of consumers take supplements every day without any apparent problems and receive health benefits. However, risks do exist, and it is important that consumers are protected. FDA does not have the authority to require supplements to undergo premarket approval for safety and efficacy. Instead, it relies mostly on its adverse event reporting system to identify safety problems.

Mr. Chairman, our review of the adverse event reporting system for dietary supplements disclosed that it is an inadequate safeguard to protect consumers. FDA lacks much of the information to effectively analyze adverse events. Specifically, the system has three major shortcomings. First, the system detects relatively few adverse event reports. Second, the system has difficulty generating signals of possible public health problems due to incomplete reports and difficulty in conducting follow-up. Third, FDA lacks the information necessary to adequately

**BACKGROUND**

In 1993, FDA created a system to collect and review adverse event reports on dietary supplements. An adverse event is an incident of illness or injury that may be associated with a product or ingredient. Reported events range in severity from nausea and dizziness to cardiac arrest or death.

Reporting adverse events associated with dietary supplements to FDA is entirely voluntary. FDA receives adverse event reports from consumers, health professionals and manufacturers through various reporting mechanisms. These mechanisms include State health departments, Poison Control Centers, direct communication with FDA and through FDA's Medwatch program, a web-based reporting system used to monitor FDA-regulated products.

FDA's adverse event reporting system for dietary supplements is an important consumer safeguard. Unlike new prescription drugs and some over-the-counter medicines, dietary supplements are not subject to premarket approval. In addition, FDA is still developing good manufacturing practices for supplement manufacturers. Instead, FDA relies largely on its adverse event reporting system to help generate signals of possible public health concerns.

We analyzed FDA's database for adverse event reports for dietary supplements received between 1994-1999. Our analysis included over 2,000 such reports. Specifically, we checked the completeness of each report in the FDA data fields. We also reviewed relevant FDA laws, regulations, policies and procedures and interviewed various FDA officials and stakeholders, including consumer and industry representatives. We conducted our review during 2000 and issued the final report in April 2001.

## RESULTS OF THE REVIEW

**FDA's adverse event reporting system detects relatively few adverse events.**

Adverse event reporting systems typically detect only a small proportion of events that actually occur. They are passive systems that depend on someone linking an adverse event with the use of a product and then reporting the event. FDA's system for dietary supplements is no exception. A study commissioned by FDA in March 2000 estimated that the agency receives less than 1 percent of all adverse events associated with dietary supplements. Our study confirmed findings in the FDA commissioned report that few events are actually reported. In fact, FDA received only 2,547 adverse event reports related to supplements between 1994 and 1999 — a period when it is estimated that more than 100 million people were taking supplements. Of particular relevance for this hearing, according to FDA's analysis, is that between 1993 and March 2000, the agency received 1,173 adverse event reports associated with products containing, or suspected to contain, ephedrine alkaloids, which are commonly used for losing weight and boosting energy.

We recognize that no clear standard exists on how many reports FDA should receive. While similar but not identical to FDA's system, Poison Control Centers, a network of sites, predominantly hospitals and academic health centers that respond to consumer calls about problems with products, appear to be receiving more reports. For the year 1999, we found that FDA received 460 reports compared to the estimated 13,000 reports that Poison Control Centers reported receiving nationwide relating to dietary supplements. Many factors may contribute to the under-reporting of adverse events for dietary supplements. First, many consumers presume supplements to be inherently safe and may fail to link an adverse event with the use of a product. Second, many consumers use these products without the supervision of a health professional who can help identify adverse events. Third, consumers may be unaware that FDA regulates dietary supplements. Fourth, FDA does not have the authority to require manufacturers to report the adverse events they receive. Finally, FDA does not conduct enough outreach to consumers, health professionals and manufacturers about the importance of reporting adverse events.

**FDA's adverse event reporting system has difficulty generating signals of possible public health concerns.**

FDA's database not only didn't contain many reports of adverse events, those reports lacked sufficient information to analyze and generate signals of public health concern. We found that FDA attempted to follow-up and obtain much needed information, such as consumer medical records, product ingredients and identity of the manufacturer to help evaluate reported events. However, the agency frequently could not obtain this necessary information. To be more specific:

*Limited medical information.* Without medical information, it is difficult for FDA to determine if the event was related to the use of the supplement. We found that FDA could not obtain medical records for 58 percent of the reports for which the agency requested. To obtain medical records, FDA first must receive permission from the alleged injured party. However, FDA told us they often have difficulty locating or reaching consumers. And even when they do reach them, consumers sometimes refuse to release medical records out of concern for their privacy. At least half of the adverse event reports that FDA receives come from consumers. Given that supplements are generally self-care products, it is not surprising that the majority of reports come from consumers. However, consumers generally are not able to provide as much medical information as health professionals. Only 27 percent of the reports come from health professionals, who are in a better position to provide important medical information and to determine if there is a relationship between the product and the event.

*Limited product information.* For 32 percent of the products mentioned in the adverse event reports, FDA was unable to determine the ingredients. FDA lacks a quick and easy reference for the name and ingredients of all products. FDA must rely on the report itself or conduct its own investigation, which can be resource intensive. In addition, because dietary supplement manufacturers are not required to prove the safety of their products prior to marketing them, FDA generally has relatively little information about the safety of particular products.

For 77 percent of the products mentioned in the adverse event reports, FDA lacked the product label. FDA often depends on the product label to determine the ingredients in a particular dietary

supplement. FDA officials emphasized the importance of obtaining the actual label from the product because some dietary supplements sold under the same name vary in the amount and type of ingredients they contain. FDA also lacked a sample for 69 percent of the products for which it requested one. Samples are sometimes necessary for further testing regarding contamination and other issues. FDA finds that it is not only difficult to locate supplement consumers, but that consumers cannot or will not provide a product sample or label. Consumers may have discarded the remaining product, may want to hold on to it pending legal action, or may have sent it back to the manufacturer for a refund.

*Limited manufacturer information.* We found that FDA could not identify the manufacturers for 32 percent of the products in its reports. Of the manufacturers in its database, FDA lacked the location for 71 percent. Manufacturers may have additional information that would be helpful to FDA. However, until recently, FDA lacked the authority to require manufacturers to register with the agency. Again, FDA does not have authority to require manufacturers to report the adverse events they receive. FDA officials estimated that it has received less than10 such reports from manufacturers. Unfortunately, we cannot confirm this, because FDA does not track this in its database. This is in contrast to the adverse event reporting system for prescription drugs and biologics, where about 90 percent of the 280,000 reports in 1999 came from manufacturers. (Prescription drug manufacturers are legally required to report adverse event reports.)

*Limited contact information on the alleged injured party.* FDA could not follow up on

27 percent of the reports it tagged for follow-up, primarily because the reports lacked enough contact information for the alleged injured party, who may be reluctant to provide such information because of privacy concerns.

*Limited ability to analyze trends.* It is difficult for FDA to conduct rigorous statistical analysis, because the agency receives relatively few reports and many are of such poor quality. Furthermore, FDA's database for analyzing adverse event reports is inadequate. The database was designed for administrative purposes rather than for trend analysis. For example, it is difficult to query the database for all reports associated with one ingredient, because all the ingredients for one product are entered into the same data field. The database also lacks automatic data edits to prevent common data entry errors, such as misspellings or illogical entries that make it difficult to perform accurate queries.

**FDA lacks the information to adequately assess signals of possible public health concerns generated by adverse event reports.**

Adverse event reports in and of themselves typically cannot generate conclusive evidence about the safety of a product or ingredient. Rather, the system generates signals that FDA must assess to confirm if, in fact, a public health problem exists. In assessing signals, FDA can rely on a variety of sources, including clinical research, scientific literature, and/or laboratory testing. However, FDA lacks many of these key tools when it comes to dietary supplements.

*Limited clinical information.* One key tool that FDA lacks in assessing signals is adequate clinical information. This information can sometimes be obtained from large-scale clinical trials, small research studies and epidemiological studies. However, the current regulatory framework for dietary supplements does not require manufactures to conduct these types of studies prior to or after marketing a product. FDA lacks the resources to conduct this type of research itself. Although some manufacturers and independent researchers have conducted such studies, these studies by no means cover all dietary supplements or ingredients. FDA has some information on the history of use, since many of these products have been used for hundreds of years. However, this information can be difficult to interpret and verify.

*Lack of information on consumer use.* The size of the consumer population and the dosages taken by consumers help FDA estimate the size of the potential threat to pubic health. Unlike prescription drugs, self-care products, such as dietary supplements, lack a formal tracking system. When FDA evaluates adverse event reports that it receives, it is difficult for the agency to know the common denominator, and, thus, the incidence of adverse events relating to a particular product or ingredient remains unknown. Consequently, this makes it difficult for FDA to determine the magnitude of the safety concern.

With limited information to draw upon to generate signals, it is not surprising that FDA rarely reaches the point of knowing whether a safety action is warranted to protect consumers. We estimated that, based on this system, FDA has taken 32 actions between January 1994 and June 2000. The two most common types of actions were (1) requesting a voluntary product recall, and

(2) issuing a warning to consumers. FDA also has disseminated letters to health professionals, required additional information on product labels, issued import alerts and seized products.

## CONCLUSION

Mr. Chairman, our review of the adverse event reporting system for dietary supplements disclosed that it is an inadequate safeguard to protect consumers.

FDA is aware of these limitations and has taken steps along the lines we have called for in our report. Similarly, dietary supplement manufacturers, the General Accounting Office, and the White House Commission on Dietary Supplements have also called for reforms. We recognize that FDA faces legislative and financial barriers to implementing many of our recommendations. Therefore, we offer our recommendations as a blueprint for action that can be taken over time. We also recognize that dietary supplements are self-care products and that they are regulated as foods. However, without some additional regulatory mechanisms in place, FDA's system will continue to fall short of its potential.

Although we made many recommendations in our report, today I would like to highlight a few key ones. We recommended that FDA seek the authority to require manufacturers to report serious adverse events to FDA for certain products. Required reporting by manufacturers would help to increase the number and quality of reports that FDA receives. This requirement need not apply to all dietary supplements, but FDA could determine the types of ingredients and products for which required reporting would be the most appropriate. We recommended that FDA receive

Poison Control Centers reports. We also recommended that FDA seek the authority to require manufacturer and product registration for all dietary supplements. A manufacturer registry would enable FDA to more quickly identify and contact manufacturers for more information when necessary. And a product registry would allow FDA to have easy access to a list of all ingredients in a particular product. The final recommendation that I would like to highlight is for FDA to develop a new computer database to track and analyze adverse event reports for dietary supplements. A new system will allow the agency to analyze reports more rigorously and easily.

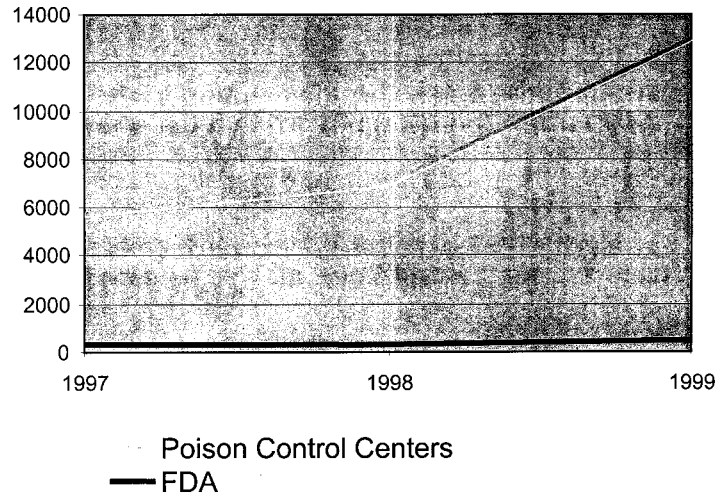
We are pleased that FDA has already taken important steps to address many of our recommendations, including the receipt of some Poison Control Centers reports and implementation of a registration system for manufacturers' facilities. In addition, FDA is currently improving its computer systems for analyzing adverse event reports.

Mr. Chairman, this concludes my testimony. I appreciate the opportunity to discuss our work regarding this important issue. We recognize that millions of consumers rely on dietary supplements. Therefore, we are committed to ensuring that FDA has the necessary tools to guarantee that the adverse event reporting system is effective in helping protect consumers.

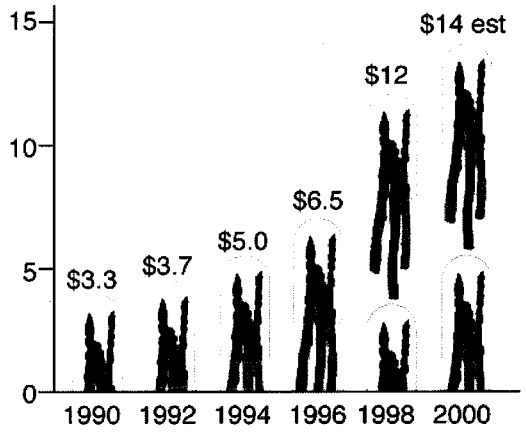
I welcome your questions.

##

**Dietary Supplement Adverse Event Reports Received by FDA and Poison Control Centers**

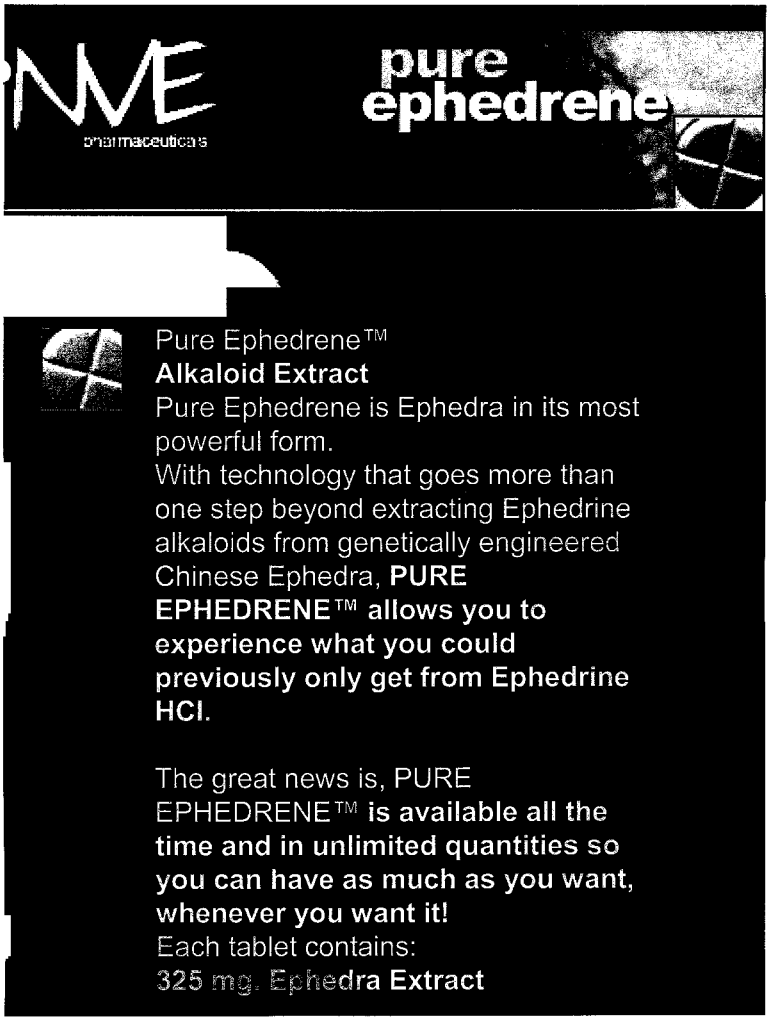



Department of Health and Human Services
Office of the Inspector General
Adverse Event Reporting for Dietary Supplements:
An Inadequate Safety Valve
OE1-01-00-00180

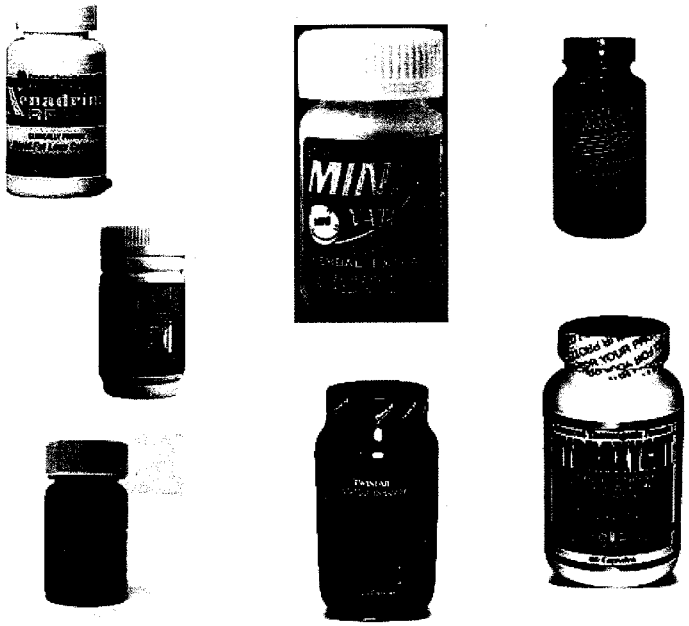



**U.S. diet-supplement sales**
**(in billions of dollars)**

*Science* 1999 Vol. 285: 1853-1855


NVE
pharmaceuticals
pure
ephedrene
Pure Ephedrene™
Alkaloid Extract
Pure Ephedrene is Ephedra in its most powerful form.
With technology that goes more than one step beyond extracting Ephedrine alkaloids from genetically engineered Chinese Ephedra, PURE EPHEDRENE™ allows you to experience what you could previously only get from Ephedrine HCl.
The great news is, PURE EPHEDRENE™ is available all the time and in unlimited quantities so you can have as much as you want, whenever you want it!
Each tablet contains:
325 mg. Ephedra Extract

# AVAILABLE IN THE US
# SUBJECT TO RECALL IN CANADA

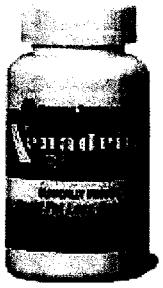


Canada has recalled all supplement products that:

- Have a dose unit of more than 8 mg of ephedrine or
- Contain ephedra/ephedrine + caffeine source or
- Make appetite suppression or increased energy claims

# AVAILABLE IN THE US


# SUBJECT TO RECALL IN CANADA

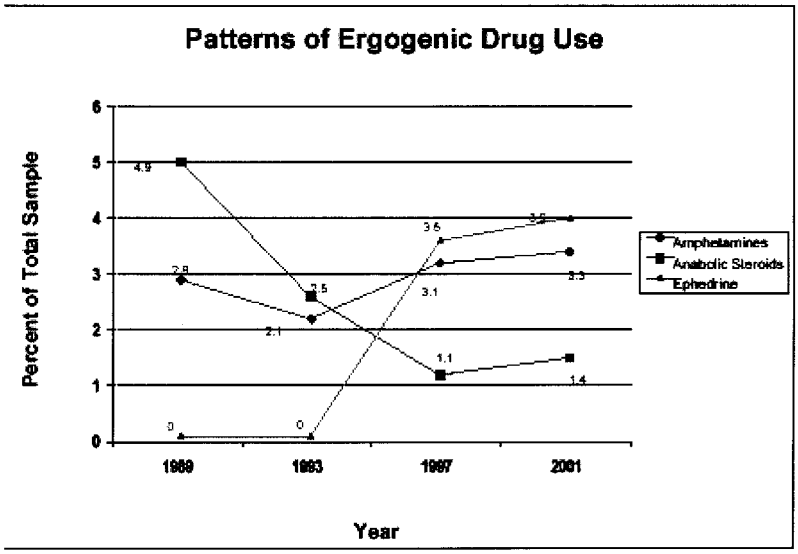


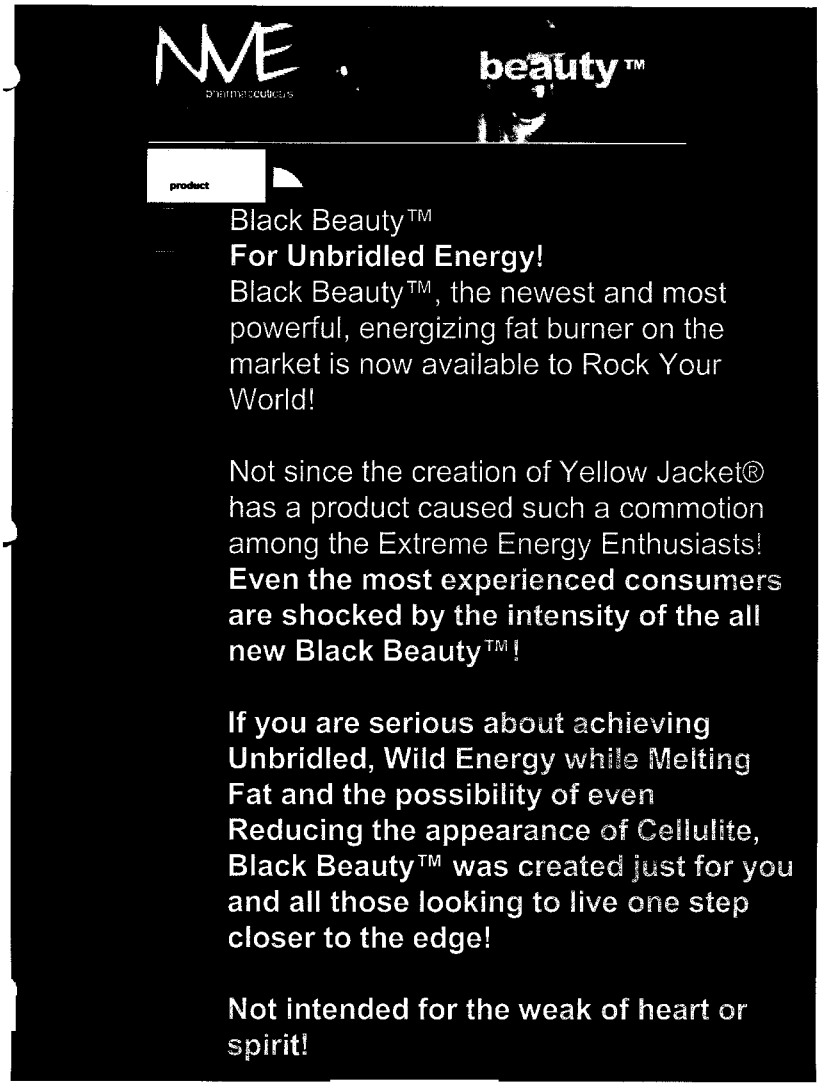
**XENADRINE® RFA-1**
**The #1 Diet Supplement in America**

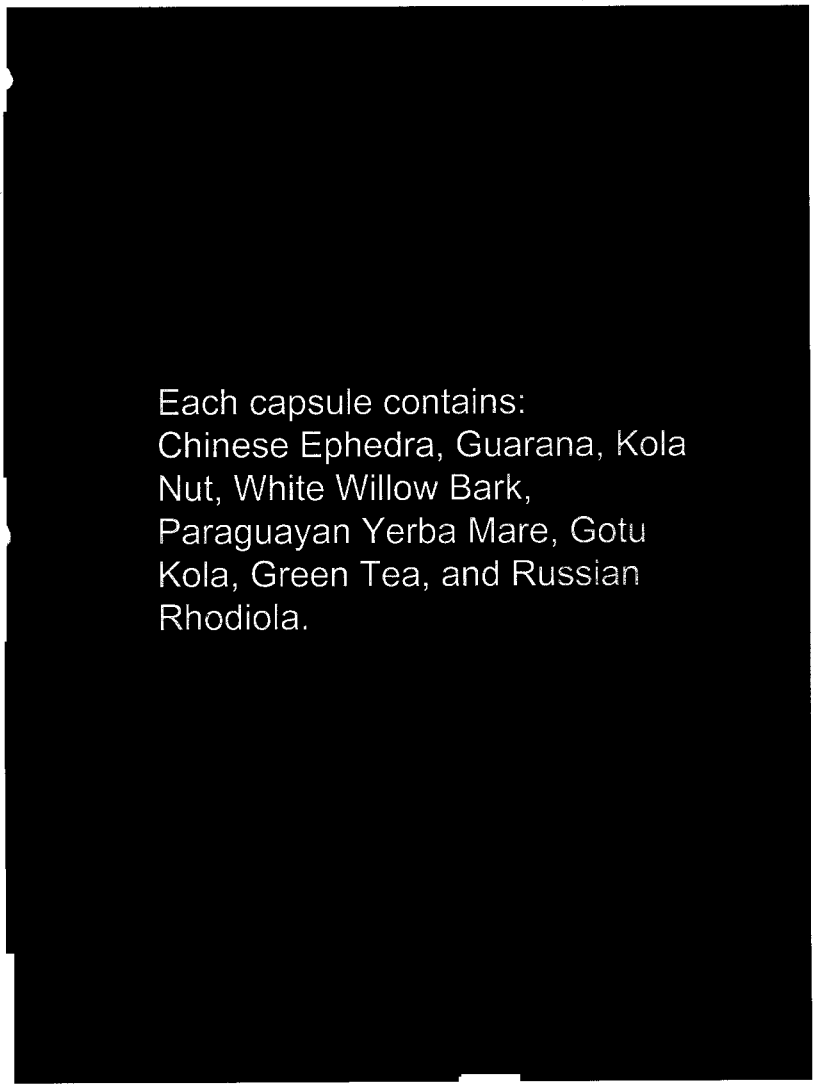
**CAUTION:** Xenadrine-RFA1 contains ephedra and may not be for everyone. This product is for adult use only and should not be used by pregnant or nursing women or by anyone with any known medical condition. Read carefully all warnings and precautions prior to use. For best results, use as part of a diet and exercise program.

# 2001 NCAA Study of Substance Use Habits of College Student-Athletes

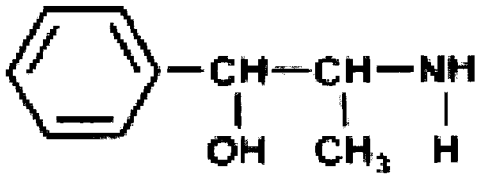
Figure 1A



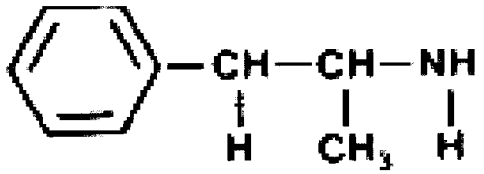

NVE
pharmaceuticals
beauty™
product
Black Beauty™
For Unbridled Energy!
Black Beauty™, the newest and most powerful, energizing fat burner on the market is now available to Rock Your World!
Not since the creation of Yellow Jacket® has a product caused such a commotion among the Extreme Energy Enthusiasts! Even the most experienced consumers are shocked by the intensity of the all new Black Beauty™!
If you are serious about achieving Unbridled, Wild Energy while Melting Fat and the possibility of even Reducing the appearance of Cellulite, Black Beauty™ was created just for you and all those looking to live one step closer to the edge!
Not intended for the weak of heart or spirit!


Each capsule contains:
Chinese Ephedra, Guarana, Kola Nut, White Willow Bark, Paraguayan Yerba Mare, Gotu Kola, Green Tea, and Russian Rhodiola.

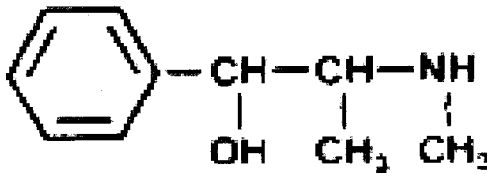
PHENYLPROPANOLAMINE




AMPHETAMINE




EPHEDRINE



Public Health Service

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

**STATEMENT OF**

**JOSEPH A. LEVITT, ESQ.**

**DIRECTOR**

**CENTER FOR FOOD SAFETY AND APPLIED NUTRITION**

**FOOD AND DRUG ADMINISTRATION**

**BEFORE THE**

**COMMITTEE ON GOVERNMENTAL AFFAIRS**

**SUBCOMMITTEE ON OVERSIGHT OF GOVERNMENT MANAGEMENT, RESTRUCTURING, AND THE DISTRICT OF COLUMBIA**

**UNITED STATES SENATE**

**JULY 31, 2002**

**RELEASE ONLY UPON DELIVERY**

Mr. Chairman, thank you for inviting me to appear before you today to discuss dietary supplements and their use for weight-loss purposes. Accompanying me today is Dr. Christine Lewis Taylor, Director of the Office of Nutritional Products, Labeling and Dietary Supplements (ONPLDS) at the Center for Food Safety and Applied Nutrition (CFSAN) and Mr. John Taylor, Director of the Office of Enforcement, Office of Regulatory Affairs (ORA) at the Food and Drug Administration (FDA or the Agency).

Before I address regulatory actions taken against unapproved drug products promoted as weight loss supplements, let me take a moment to explain the regulatory and enforcement programs that FDA uses to implement the Dietary Supplement Health and Education Act (DSHEA or the Act) and Agency efforts to implement DSHEA in the eight years since it became law.

**A DIFFERENT TYPE OF FDA PROGRAM**

When Congress passed DSHEA, it created a unique regulatory framework for dietary supplements. Its purpose was to strike the right balance between providing consumers access to dietary supplements that they use to help maintain and improve their health and giving FDA the regulatory authority to take action against supplements that present safety problems or have false or misleading labeling.

The DSHEA regulatory framework for dietary supplements is primarily a postmarket program, as is the case for foods in general. Since Congress considered dietary

ingredients marketed prior to the passage of DSHEA to be safe, dietary supplements containing these ingredients are permitted to be freely marketed, just like regular foods (e.g., fresh fruits and vegetables, processed foods and beverages, and seafood). Should safety problems arise after marketing, the adulteration provisions of the statute come into play. Under DSHEA, a dietary supplement is adulterated if it or one of its ingredients presents "a significant or unreasonable risk of illness or injury" when used as directed on the label, or under normal conditions of use (if there are no directions). The burden of proof is on FDA to show that a product or ingredient presents such a risk. In addition, the Secretary of Health and Human Services (HHS) may also declare that a dietary supplement or dietary ingredient poses an "imminent hazard" to public health or safety.

In 1999, in Congressional testimony before the House Government Reform Committee, the FDA Commissioner stated, "It is clear, with the benefit of hindsight, that we still have a way to go both in achieving full implementation of DSHEA and in developing a workable regulatory framework." Based on that assessment FDA decided to take a step back, as if DSHEA had just been enacted, and lay out a long-term comprehensive framework to fully implement the statute. We embarked on a year-long process for FDA to formulate a roadmap of activities to fully implement DSHEA. I personally led this process which included considerable interaction with stakeholders.

**STAKEHOLDER INPUT**

Obtaining stakeholder input on dietary supplement issues and exchanging ideas with stakeholders on how best to address those issues is a high priority for FDA. To this end,

we held two public meetings with stakeholders in the summer of 1999 - one in Washington, DC and one in Oakland, CA - to provide the dietary supplement community the opportunity to identify key issues and how they would like FDA to address these issues. These meetings provided the stakeholders an active role in developing an effective dietary supplement regulatory program. I chaired both meetings.

Overall, the stakeholders' major emphasis was on safety. "Safety first" was a frequent comment. Examples of stakeholders' recommendations include: 1) improving FDA's Adverse Event Reporting System (AERS); 2) publishing regulations on Good Manufacturing Practices (GMPs); 3) creating a stronger scientific foundation for regulating these products; and 4) leveraging outside resources. A number of participants placed a great deal of emphasis on FDA taking stronger action to ensure the safety, composition, and proper labeling of dietary supplement products, with a particular emphasis on safety. Many stakeholders called for greater enforcement of DSHEA.

FDA established five strategy teams to consider the ongoing stakeholder input and to discuss the dietary supplement activities needed to fully implement DSHEA. These teams covered the following topics: safety, labeling, boundaries, enforcement and research. The strategy team members were drawn from several FDA units, including CFSAN, the Center for Drug Evaluation and Research (CDER), ORA, and the Office of the Chief Counsel. A section on outreach was added later and the research category was broadened and renamed "science base." These categories formed the organizational structure of the Dietary Supplement Strategic Plan (DSSP). With the identification of

stakeholders' major interests and concerns about DSHEA driving the creation of FDA strategy teams, our process to accomplish a long-term implementation strategy began.

**THE DIETARY SUPPLEMENT STRATEGIC PLAN**

On January 3, 2000, the Agency launched its DSSP. The plan is designed to be implemented in stages. Its foundation rests on both law and science.

The DSSP goal has four overall themes:

- Fully implement DSHEA. There was considerable concern within the industry that FDA would not "accept" DSHEA. The Agency clearly understands that Congress passed DSHEA and it is FDA's job to implement it as fully as possible.
- Implement DSHEA in a science-based way. This is the underpinning of all of FDA's successful programs, and FDA needs to use that same model here. A science-based model leads to greater objectivity in decision making and greater public confidence in FDA's actions.
- Achieve a high level confidence in the safety, composition, and labeling of dietary supplement products. It is the compass that should guide FDA.
- Engage in a long-term effort. Although implementation is underway, this is an ambitious undertaking. The strategic plan lists 35 issues to address within six broad categories. Moreover, resource availability will play a pivotal role in how long or short the implementation process will be.

Accordingly, the Strategic Plan's Goal Statement reads: "By the year 2010, have a science-based regulatory program that fully implements the Dietary Supplement Health and Education Act of 1994, thereby providing consumers with a high level of confidence in the safety, composition, and labeling of dietary supplement products."

FDA recognizes the success of the strategy will depend on new and continued partnerships with other government agencies, academia, health professionals, industry and consumers. The Agency is committed to continue its outreach to stakeholders by establishing stronger working relationships with them as well as leveraging resources, and communicating accurate dietary supplement information. The DSSP can be accelerated or decelerated, depending on resource availability and safety concerns.

The Strategic Plan is divided into six sections, consistent with the stakeholders' input that FDA received:

1. Safety
2. Labeling
3. Boundaries
4. Enforcement
5. Science Base
6. Outreach

**1. Safety - AERS and GMPS**

Virtually every stakeholder urged us to address "safety first." Because of DSHEA's postmarketing emphasis, FDA needs an effective AER monitoring system to identify and respond to potential health risks to consumers associated with the use of dietary supplements. FDA's AERS for dietary supplements provides an essential tool for signaling potential safety problems that may be associated with the use of a particular product or type of products that needs to be investigated and critically evaluated.

For example, in March 2002, FDA issued a consumer alert about kava-containing dietary supplement products and the potential risk of serious liver injury. The basis for this alert was a review of adverse event reports involving kava kava from the U.S. and Europe by FDA health care professionals. In the U.S., FDA had received a report of a previously healthy young female, who after using kava, required a liver transplant. In other countries, approximately 25 adverse events had been reported, four of which resulted in liver transplants. In addition, the Europeans had reported a documented case of hepatic toxicity in an individual who retook the kava-containing product even after experiencing an initial reaction. Taken together, this information warranted a consumer alert. FDA urged persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver, to consult a physician before using kava-containing supplements.

In April 2001, the Office of the Inspector General (OIG) of HHS provided a number of useful recommendations for enhancing the quality and capability of FDA's AERS for dietary supplements.

CFSAN has embarked on a significant effort to enhance its AERS through the development of the new CFSAN Adverse Event Reporting System (CAERS). Inherent in the design of CAERS is the capture and analysis of all reports of consumer complaints and adverse events related to CFSAN-regulated products, particularly dietary supplements. This system will incorporate all existing Center adverse events reporting systems into one state-of-the-art reporting and monitoring system. The CAERS staff will work closely with program experts throughout FDA and other governmental agencies, and with industry, professional organizations, and other interested parties. CAERS is in its developmental stages. With new funding of 2.5 million dollars provided in the Fiscal Year (FY) 2002 budget, FDA will be able to pilot-test the new system this fiscal year.

There is broad public support for dietary supplements GMPs to enhance public confidence in these products. As a preventative measure, DSHEA grants FDA explicit authority to establish GMP regulations for dietary supplements. Such regulations are critical to assuring quality, purity, and consistency in dietary supplement products. FDA has made the publication of a GMP proposed rule a high priority and we are in the final stages of that process. We will conduct an outreach program after the publication of the proposed rule. Instituting a credible GMP system will require that FDA have enough

field investigators for inspections to ensure that industry is manufacturing products in accordance with the GMPs.

**2. Labeling**

One of the challenges FDA faces is to strike the right balance between preserving consumers' access to products and information, and assuring the safety and proper labeling of all these products. At the public meetings we held in 1999, the stakeholders clearly expressed the view that labeling was a major problem and an area that FDA should emphasize as it worked to ensure public confidence in these products. When products are not labeled accurately or are labeled in a misleading way, consumers do not readily know what they are getting when they take these products.

For example, stakeholders raised concerns that consumers do not understand that dietary supplements can interact in a harmful way with medications they may be taking, such as prescription or over-the-counter (OTC) drugs, and that it is important to discuss dietary supplement consumption with their healthcare providers. In addition, certain populations such as pregnant or lactating women, infants and young children, and the elderly are more vulnerable to potential adverse effects from dietary supplements. Many stakeholders want labels to include information that addresses potential drug/dietary supplement interactions and to discuss concerns related to specific, potentially more vulnerable populations.

FDA heard concerns from some stakeholders about labeling claims and substantiation of claims. Many stakeholders believe that there are products on the market with false or misleading claims, and that the line between labeling and advertising/marketing increasingly has become blurred through direct-to-consumer advertising and through the Internet. Stakeholders also believe that FDA had not used its authority to enforce DSHEA with respect to labeling claims and substantiation.

DSHEA allows the use of certain claims (often called structure/function claims) of general well being from consumption of a dietary ingredient, and claims of benefits related to classical nutrient deficiency diseases. These claims require the manufacturer to notify FDA within 30 days of marketing. Manufacturers must have substantiation that the claims are truthful and not misleading, and the product label must bear the statement "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." FDA published a final "structure/function" regulation in January 2000.

FDA reviews proposed health claims for dietary supplements under the provisions of the Nutrition Labeling and Education Act of 1990 (NLEA), implementing regulations and relevant case law. A number of dietary supplement health claims are authorized by regulation, including claims for calcium and reduced risk of osteoporosis and for psyllium and reduced risk of heart disease. By law, claims that a dietary supplement treats or mitigates a disease may not be made unless the supplement is approved for that use under the new drug provisions of the Federal Food, Drug, and Cosmetic (FD&C) Act.

DSHEA also contains a "premarket" provision which covers dietary supplement manufacturers that wish to market certain new dietary ingredients. New dietary ingredients are those that were not marketed in the U.S. before 1994, and that have not been in the food supply as articles used for food without chemical alteration. Dietary supplement manufacturers must submit to FDA, at least 75 days before the product is expected to go on to the market, information that supports the conclusion that a supplement containing the ingredient will reasonably be expected to be safe. After the 75-day period has expired, there is no requirement that the manufacturer receive FDA approval or clearance before marketing the product. It is essential for public health protection that FDA have the resources to review the notifications in a timely manner. So far, we have been able to meet our review deadlines. However, our workload may increase as, with the passage of time, the industry seeks to market more new dietary ingredients.

Finally, stakeholders pointed to recommendations made by the Commission on Dietary Supplements Labels on November 24, 1997. Stakeholders wanted FDA to use those recommendations as a blueprint for addressing many of the labeling concerns that still exist today.

**3. <u>Boundaries</u>**

The boundaries section highlights one of the profound challenges of DSHEA - determining the regulatory category of a product. It is important to draw boundaries between dietary supplements, drugs, and conventional foods and to give manufacturers

notice of the regulatory regime that applies to their products. FDA's "structure/function" rule, referenced above, began to address the drug/supplement boundary issues.

**4. Enforcement**

The plan also outlines FDA's enforcement priorities, with safety as a top priority. This section also includes activities devoted to improving FDA's internal capacity in the enforcement area.

Industry clearly was concerned that FDA had not been sufficiently proactive in taking action against violative products on the market. They said the whole industry is affected by the few "bad actors" marketing unsafe products or products with misleading and untruthful claims, and this undermines consumer confidence. Industry wanted FDA to take enforcement action, where appropriate, so there is a "level playing field" and so consumers will have confidence in the dietary supplement products that do provide benefits. In addition, industry wanted FDA to especially focus its enforcement action on those products whose claims are most egregious.

Consumers also wanted stronger FDA enforcement action. These stakeholders wanted FDA to be more assertive with respect to challenging product claims for substantiation, both in cases where the products presents safety issues and in cases where the products may not provide the benefits they allege they can.

Some specific enforcement activities are discussed later.

***Pearson v. Shalala* Health Claims Policy**

The U.S. Court of Appeals for the District of Columbia, in *Pearson v. Shalala*, ordered FDA to clarify its Significant Scientific Agreement (SSA) standard, reevaluate four claims the Agency had previously denied, and permit health claims that do not meet the SSA standard if a disclaimer can ensure that the claim will not mislead consumers.

The Agency has made considerable progress here. After issuing guidance clarifying the SSA standard and holding a public meeting, FDA published (in the *Federal Register* of October 6, 2000) its current strategy for implementation of the decision. This strategy includes providing enforcement discretion for qualified claims that meet designated criteria.

There have been 14 dietary supplement health claims considered by FDA subsequent to the *Pearson* court case. Of these, six claims were considered for qualified claims; six claims were denied or withdrawn prior to Agency consideration of permitting qualified claims; and two more claims are still under initial review.

**5. Improving the science base**

The science base section is the most important component of the plan because, like all FDA-regulated products, public credibility comes with knowing there is an adequate scientific foundation to the products and their claims. However, it is also the least well-developed section of the plan. Unlike conventional foods, FDA has limited experience and expertise with dietary supplement ingredients.

Stakeholders emphasized the importance of creating a stronger scientific foundation for regulating dietary supplements. FDA believes this to be the most important factor in the success of this program over the long-term if consumers are to have sustained confidence in these products. Accordingly, strengthening the science base is a critical element in the DSSP, just as it is with all of FDA's programs. The science base for a number of dietary supplements is starting to increase. FDA needs to take advantage of available science while promoting research to continually enhance its knowledge in this area. FDA believes very strongly that there needs to be a strong science base underpinning the regulatory program.

Stakeholders encouraged FDA to leverage outside resources to improve the science base. FDA is developing a broad dietary research agenda because we recognize the long-term success of the dietary supplement program is dependent on the strength of the scientific underpinning for these products. FDA will need to work very closely with the National Institutes of Health (NIH), industry, academia, and other Federal, State, and local agencies to ensure that the goal is met through leveraging and partnerships. We need to make sure the right research is undertaken and the right questions are answered. For example, we are working closely with the Office of Dietary Supplements and the National Center for Complementary and Alternative Medicine at NIH.

In FY 2001, Congress appropriated one million dollars in FDA's budget for collaborative research between FDA and the National Center for Natural Products Research (NCNPR) at the University of Mississippi. NCNPR is nationally and internationally recognized for

its expertise and research experience in botanicals used for health purposes. The NCNPR mandate is to bring government, academia, industry, consumers, health professionals and industry together to solve scientific problems in this area. We are enthusiastic about this new partnership and hope to be able to expand it in future years. An additional one million dollars has been appropriated for FY 2002.

Last year FDA entered into a contract with the Institute Of Medicine (IOM) at the National Academy of Sciences entitled, "Framework for Evaluating the Role of Dietary Supplements in Health." The IOM will develop a protocol for the Agency to use in reviewing the safety of dietary supplements. The contract requires that the IOM constitute a committee that will:

- Develop a proposed framework for categorizing and prioritizing dietary supplement ingredients based on safety issues;
- Describe a process for developing a review system with specifications for evaluating the safety and role in health of dietary supplement ingredients; and
- Develop at least six prototypes as examples of using the proposed framework.

The framework will include a methodology to examine the available peer-reviewed literature with regard to the role of dietary supplement ingredients in health. Methods that other expert bodies have used to categorize and review issues related to safety and the possible roles of dietary supplements and their ingredients in health will also be taken into consideration. The IOM process includes opportunities for public input. On

July 24, 2002, the Academy released the draft framework for public comment. Comments will be taken through September 30, 2002. The Agency now expects the final report in March 2003.

**6. Outreach**

Finally, the Outreach section of the plan reflects FDA's continued commitment to a two-way dialogue with the dietary supplement community. Communication with the general public, FDA field offices, health care professionals, and industry in an appropriate and timely manner is critical, particularly when information relates to potential adverse effects associated with dietary supplements. FDA will continue its commitment to establish a stronger working relationship with organizations interested in promoting two-way communication and cooperation. As a result of input from FDA's stakeholders and the increasing scope of the scientific questions concerning dietary supplements, a standing Dietary Supplement Subcommittee was recently added to FDA's restructured Food Advisory Committee. We are in the process of scheduling the subcommittee's first meeting.

**CHALLENGES SINCE DSHEA**

There have been many changes in the size and scope of the industry and in consumer use of dietary supplements since the 1994 enactment of DSHEA.

**Dietary Supplement Consumption**

A survey by PREVENTION Magazine on Consumer Use of Dietary Supplements in 2000 shows that over 158 million consumers use dietary supplements. The same survey states that "an estimated 115.3 million consumers buy vitamins and minerals for themselves, and 55.8 million purchase them for other members of their family, including children."

The basic reason cited for dietary supplement growth is the desire for self-care. According to the PREVENTION Magazine survey, consumers use dietary supplement products to help them achieve their self-care goals, which arise out of a sense of alienation from the established health care system. Results from a national survey conducted in 1999 by Men's Health magazine show that consumers use dietary supplements as a means of ensuring good health. They also use supplements for very specific, medicinal purposes such as treating and preventing serious illnesses, colds, and the flu; increasing mental sharpness; and alleviating depression (PREVENTION Survey).

The consumer's desire for self-care and the widespread use of dietary supplements may cause problems for public health. Many consumers put themselves at risk from misuse of dietary supplements and the possibility of interaction effects with prescription and OTC products. An estimated 22.8 million consumers use herbal remedies instead of prescription medicine, and an estimated 19.6 million use them with a prescription product, according to the same PREVENTION Magazine survey. According to the

National Business Journal, 2000, dialog File No. 93, herbals and botanicals incorporate 32 percent of the estimated 17.1 billion dollars dietary supplement market for the year 2000, with vitamins slightly higher at 38 percent, as referenced in Illustration 3 (National Business Journal, 2000, Dialog File No. 93, San Francisco: The Dialog Corporation, 2000).

**Size and Scope of the Industry**

The dietary supplement industry is one of the fastest growing industries in the world consisting of 1,566 establishments, as referenced in Illustration 1 ("Survey of Manufacturing Practices in the Dietary Supplement Industry: Final Report," RTI Task Order No. 6, May 17, 2000). Dietary supplement sales reached 14.1 billion dollars in 1998 and are estimated to reach 15.5 billion dollars for 1999 and 17.1 billion dollars for 2000, as referenced in Illustration 2 ("US Dietary Supplements Market Size Expressed as Dollar Sales by Top Six Product Categories for 1994 to 1998 and Forecast for 1999 and 2000"; National Business Journal, 2000, Dialog File No. 93, San Francisco: The Dialog Corporation, 2000). In 1999, consumers spent nearly double the amount spent in 1994, and sales continue to grow at more than 10 percent a year (Nutrition Business Journal, San Diego, 1998).

**Scope and Access to the Products**

In the past, except for vitamin and mineral products, dietary supplements, particularly botanical products, were mainly sold to adults in health food stores. In contrast, such products are now available in supermarkets, other retail stores, and on the Internet, making these products readily accessible to children and other vulnerable populations. The Nutrition Business Journal estimated that in 1999 U.S. consumer sales of supplements over the Internet amounted to 142 million dollars, almost three times the previous year's total of 48 million dollars ("E-Commerce in the Nutrition Industry," Nutrition Business Journal, Volume No. 4, April 2000).

**REPORT TO CONGRESS**

Congress asked FDA to identify the level of funding that would be necessary to fully implement DSHEA as outlined in the DSSP. In May 2002, FDA provided Congress with a "Dietary Supplement Strategic Plan Cost Out."

In this report, FDA estimates the initial investment cost to implement the goals in the Strategic Plan would be a range from 25 million to 40 million dollars by Year 3, increased to 30 million to 55 million dollars by Year 4, and completed at 40 million to 65 million dollars by Year 5. These estimates are reported in FY 2002 current dollars.

**ENFORCEMENT**

Congress defined the term "dietary supplements" in DSHEA. A dietary supplement is a product that is ingested, is intended to supplement the diet and, among other requirements, contains a "dietary ingredient." The "dietary ingredients" in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and dietary substances such as enzymes. Dietary ingredients also can be metabolites, constituents, extracts, concentrates, or combinations of the preceding types of ingredients. Dietary supplements may be found in many forms, such as tablets, capsules, liquids, or bars. Information on their label must not represent the product as a conventional food or a sole item of a meal or diet. Instead, DSHEA placed dietary supplements in a special category under the general umbrella of "foods" and requires that every supplement be labeled as a dietary supplement.

**Agency Actions Based on Dietary Supplements Definition**

When a problem arises with a product regulated by FDA, the Agency can take a number of actions to protect the public health. For dietary supplements, as with other products, initially, the Agency works with the marketer of the product to correct the problem voluntarily. If that fails, the Agency can also ask the marketer to recall a product voluntarily. The Agency can also seek, through the courts, seizure of violative products and/or injunction against firms or individuals who market violative products, and detain or refuse entry of products presented for import at U.S. ports. When warranted, criminal penalties - including prison sentences - are sought through the courts, as well as against those who violate the law.

The Agency's ORA works in close cooperation and coordination with all of FDA's Centers (the Centers) in enforcing the law. With regard to health fraud specific to dietary supplements, CFSAN has the lead and is responsible for the oversight of dietary supplements. CDER also has a role to play, as many of the most successful cases the Agency has brought concerned products purporting to be dietary supplements that were actually drugs within the meaning of the FD&C Act and failed to meet the regulatory requirements for drugs prior to their introduction into interstate commerce. The Agency has a number of ongoing activities directed at combating health fraud.

FDA has taken several enforcement actions pertaining to dietary supplements. These include actions related to products containing aristolochic acid and comfrey, obtaining injunctive relief in the case of products containing tiratricol, and actions against LipoKinetix. FDA took action against these products because they did not contain dietary ingredients identified in DSHEA and/or because they were promoted to treat a disease or presented safety concerns. In FY 2002, Congress appropriated 500,000 dollars for dietary supplement enforcement efforts.

**United States v. Syntrax Innovations, Inc., et al.**

This case involved a drug called Triax Metabolic Accelerator, marketed by Syntrax as a dietary supplement for the treatment of obesity and to promote weight loss. FDA scientists determined that Triax posed a serious health hazard to those who consumed the product. The product contained triatricol, a potent thyroid hormone, that FDA medical review identified as a hazardous compound that could cause heart attacks and strokes.

FDA alleged that Triax could not be a dietary supplement because it was promoted to treat a disease (obesity) and because it did not contain any of the dietary ingredients identified in the definition set forth in DSHEA.

This case began as a seizure by the Department of Justice (DOJ), but the government amended the complaint to request injunctive relief. Syntrax originally contested the case, but later conceded that Triax is a drug. On February 14, 2001, a District Court Judge entered an order of injunction to prevent the distribution of Triax by Syntrax Innovations. In 1999 and 2000, the Agency brought seizure actions against three other weight loss products that contained tiratricol.

**E'OLA International, Inc.**

At the request of FDA, U. S. Marshals seized unapproved drug products from Biogenics Inc., of St. George, Utah, doing business as E'OLA International, and at its contract manufacturer, Nature's Energy, Inc., of Pleasant Grove, Utah. About 140,000 bottles of AMP II Pro Drops valued at 2.8 million dollars were seized, along with the bulk ephedrine hydrochloride (HCl) used in its manufacture. Although the finished products contained the drug, ephedrine HCl, they were labeled as dietary supplements for use in weight loss. The products, however, do not meet the definition of a dietary supplement because ephedrine HCl is not a dietary ingredient under the Act. FDA inspections of E'OLA revealed that the firm purchased raw materials and ephedrine HCl, had other firms produce AMP II Pro Drops on contract, and then had them ship the finished product back to E'OLA for distribution.

Ephedrine HCl has been approved as a drug by FDA since 1948 and, therefore, cannot be legally marketed as a dietary supplement. In addition, E'OLA marketed AMP II Pro Drops as a treatment for obesity. Dietary supplements cannot be marketed to treat obesity, a disease. These products also were misbranded because their labeling fails to bear adequate directions for use as is required of all drug products.

In April 2002, a District Court Judge signed a Consent Decree that prohibited Biogenics, Inc., from doing business as E'OLA from holding, manufacturing, processing, packing, labeling, promoting, or distributing AMP II Pro Drops or any other product containing ephedrine HCl or synthetic ephedrine.

**Nature's Nutrition Formula One**

FDA determined that this pre-DSHEA product, which was marketed between 1992 and 1994, as an all natural "nutritional supplement" that contained plant ingredients, was actually made with two pharmaceutical-grade chemicals, ephedrine hydrochloride and caffeine anhydrous. FDA received more than 100 reports of injuries and adverse reactions related to the product, ranging from serious and life-threatening conditions, such as irregular heartbeat, heart attack, stroke, seizures, hepatitis and psychosis, to relatively minor and temporary conditions such as dizziness, headache and gastrointestinal distress. At least one death was associated with the use of this product.

This case was developed by the alerts provided from the adverse event reports, by ORA's field staff, and by the work of the Office of Criminal Investigation (OCI) with DOJ.

FDA learned that the Chemins Company, Inc., which manufactured the product, went to great lengths to hide its actions from the Agency and concealed the actual ingredients of Formula One. As a result, the government launched a criminal prosecution against the company and its president, James Cameron.

On July 7, 2000, a Federal judge sentenced James Cameron to 21 months in jail and fined him and this corporation 4.7 million dollars. In his plea agreement, Mr. Cameron admitted that he and his company labeled Formula One as "all natural" but secretly spiked the product with synthetic ephedrine hydrochloride and caffeine anhydrous. He also admitted that the product's labeling failed to disclose the use of the chemicals on the list of ingredients, and that he and his employees had misled FDA investigators and hindered inspections of Chemins. The sentence marked the culmination of a three-year investigation. Mr. Cameron, whose company continues to make dietary supplements, began serving the sentence in September 2000.

**Other Enforcement Actions**

In addition, FDA and DOJ have pursued seizures of a number of unapproved drugs that have been promoted on the Internet as dietary supplements, including GBL and 1, 4 butanediol. FDA also has sought product recalls and achieved the voluntary destruction of 18 products containing these substances.

## Other Activities to Combat Health Fraud

### Health Fraud Working Groups

In 1992, FDA began sponsoring a National Health Fraud Working Group. The Working Group is currently comprised of representatives from the Association of Food and Drug Officials, State Attorneys General, Federal Trade Commission (FTC), Health Canada, and FDA representatives from the Center and field offices. This group meets on a regular basis to facilitate the coordination of regulatory activities, information exchange, and leveraging of each member agency.

### Health Fraud Workshops

In July 2001, FDA, FTC and the Association of Food and Drug Officials sponsored a "Health Products Fraud Investigations and Law Enforcement: Building Partnerships Workshop" in San Antonio, TX.

The workshop provided an opportunity for attendees from Federal, State, and local regulatory and law enforcement agencies in the U.S., Canada, and Mexico to share their methods for regulating and prosecuting deceptive and fraudulent promotion of health products and services. The workshop helped the participants identify and leverage methods of enforcement. The workshop helped participants identify areas for coordination and cooperation with other agencies.

Building on the successful outcomes of the San Antonio workshop, FDA and FTC sponsored a "Health Fraud Summit" in Washington, DC on May 29, 2002. This meeting provided more than thirty management-level participants from twelve Federal/State regulatory and law enforcement agencies in the U.S. and Canada with an opportunity to come together to develop procedures to improve and strengthen interagency cooperation. The regulation of dietary supplements and the fraudulent marketing of dietary supplements were discussed at both meetings.

**"Operation Cure.All"**

FDA also has enhanced its cooperation with FTC, through "Operation Cure.All" and other efforts. In 1997, FTC, FDA, Health Canada, and various State Attorneys General organized and implemented an ongoing and comprehensive law enforcement and consumer education campaign against the fraudulent marketing of supplements and other health products on the Internet. The agencies have moved to stop Internet scams for supplements and other products that purport to cure cancer, HIV/AIDS, and countless other life-threatening diseases.

FDA has made Internet surveillance an enforcement priority. The Agency's partnership with FTC, and others, in "Operation Cure.All" further demonstrates FDA's commitment to monitoring violative conduct on the Internet. Collaboration on all "Operation Cure.All" activities maximizes FDA's effectiveness in communicating to the Internet community that the various regulatory and law enforcement agencies are working together to combat health fraud. All activities are coordinated in order to ensure

consistent results in areas where FTC, FDA, the States, and Health Canada have jurisdiction.

Since the inception of the original Operation Cure.All campaign there have been three Internet surfing campaigns. In October 2001, a coordinated FDA and FTC Internet "surf" found Internet sites touting products and therapies that claim to prevent, treat, or cure anthrax, smallpox, and other health hazards. The Internet search focused on products claiming to protect against, detect, prevent, or treat biological and chemical agents, including anthrax.

The campaign was based on information gathered by FTC and FDA, more than 30 State Attorneys General, and the California Department of Health Services. More than 200 sites marketing bioterrorism-related products were uncovered. Included were 50 sites selling dietary supplements such as colloidal silver, zinc mineral water, thyme, and oregano oil as treatments for contamination by biological agents. FTC sent e-mail warnings to these operators telling them to pull the misrepresentations that any diet supplement could be used to cure anthrax. FDA sent warnings to nine Internet sites selling the antibiotic ciprofloxacin for the treatment or prevention of anthrax.

Since its inception, "Operation Cure.All" has resulted in hundreds of advisory letters directed at sites selling products with egregious claims as well as many enforcement actions directed against the marketing of fraudulent products. FDA sent cyber-letters to 48 sites selling colloidal silver products with egregious disease claims. And FDA sent a

letter to manufacturers of products containing comfrey, which is associated with liver damage and other health hazards, advising them not to use this ingredient in dietary supplements.

The Agency has engaged in several consumer education efforts with FTC including a "Miracle Health Claims: Add a Dose of Skepticism" health fraud brochure. The brochure helps the consumer in spotting false and unsubstantiated claims and has suggestions on how to avoid being the target of health fraud.

**Other Internet Activities**

Over the past several years, FDA has sharpened its focus on the issue of Internet promotion and sale of drugs as online activity has expanded. In 1996, and again in 1999, FDA held public meetings to discuss and examine the issue of promoting, prescribing, and dispensing drugs online.

In January and February 2002, an Internet surf was conducted as part of an International Internet surf, led by the Australian Competition and Consumer Commission and with participation by 19 members of the International Marketing Supervision Network, an organization made up of consumer protection agencies worldwide. As a result of the surf, FTC has sent over 280 advisory letters to domestic and foreign sites that were identified as making questionable claims for health-related products or services including dietary supplements. FDA also is making initial contact with Internet sites and alerting them to potential legal problems. The websites FDA visited promote dietary supplement

products for treatment of diseases to include arthritis, cancer, and HIV/AIDS. As a follow up, CFSAN will be revisiting these sites to verify whether the website operators made corrective actions. FDA is planning follow up as appropriate. In addition, FDA and FTC are evaluating the responses to these advisory letters and they will coordinate appropriate enforcement actions if they are necessary.

In July 1999, FDA adopted, and has since been implementing, an Internet Drug Sales Action Plan to expand and improve its activities in addressing the unlawful sale of drugs over the Internet. The illegally marketed drugs targeted by the plan include a variety of fraudulent products, including counterfeit drugs, drugs marketed with fraudulent health-related claims, and unapproved new drugs masquerading as dietary supplements. The plan is based on internal deliberations, meetings with Federal and State regulatory and law enforcement bodies, as well as organizations representing customers, health care practitioners, and the pharmaceutical and pharmacy industries. The elements of the plan include, among others:

- **Public Outreach:** FDA Talk Papers, articles in the FDA Consumer magazine, and information on FDA's website to help educate consumers about safely purchasing drugs online.
- **Professional Outreach and Partnering:** Periodic meetings with State and Federal regulatory and law enforcement bodies, consumers, health care practitioners, and industry to share information and strategize about how to address the challenges the Internet presents.

- **Coordinating Activities with other State and Federal Agencies:** Established cooperative working relationships with DOJ, the Drug Enforcement Administration, the Federal Bureau of Investigation, FTC, U.S. Postal Service, U.S. Customs Service, and other appropriate Federal and State law enforcement agencies.
- **International Cooperation:** FDA and other Federal agencies must work with foreign governments to bring action against foreign-based sellers.

Under DSHEA, FDA will take appropriate action against unsafe products, inaccurate and misleading labeling and consumer fraud. FDA will also conduct marketplace surveillance and monitoring activities. FDA will establish partnerships with Federal, State, and local agencies to enhance enforcement efforts by sharing data, heightening communication, and utilizing resources.

FDA is committed to identifying and taking action on products that present safety hazards. In September 2001 testimony before the Senate Committee on Aging, FDA's Director of the Office of Enforcement stated, "While we are first and foremost a science-based public health agency, we also are a law enforcement agency... Strong law enforcement tools - including a cadre of seasoned law enforcement agents and sufficient statutory authority - coupled with a strong base of medical and scientific expertise to evaluate marketed health products are vital to the Agency's ability to meet its mission of protecting the public health."

**Recent Developments**

On June 14, 2002, HHS Secretary Tommy Thompson announced plans to expand scientific research on the safety of ephedrine alkaloids and to aggressively pursue the illegal marketing of non-herbal synthetic ephedrine alkaloid products. As part of these efforts, FDA sent six warning letters to firms unlawfully selling non-herbal ephedrine-containing products over the Internet. Six letters went to manufacturers of products that contain the drug ephedrine or norephedrine hydrochloride (a synthetic, non-herbal, version of the herbal ingredient ephedra) labeled as dietary supplements for use in weight loss, suppression of appetite, enhanced libido, and the like. These products violate the law because they are not legal dietary supplements and are illegal drugs. Also, FDA warned another company for illegally promoting its ephedrine product as an alternative to street drugs.

HHS recently funded the RAND Corporation to conduct a comprehensive review of the existing science on ephedrine alkaloids, particularly those in dietary supplements. The review should be completed this fall. NIH will use this information, which will clarify the existing state of the science on ephedrine alkaloids, to guide an expanded research effort to better understand the safety of ephedrine alkaloids.

**CONCLUSION**

FDA will continue to work collaboratively with other governmental agencies, academia, health professionals, industry, and the Congress so that we all can be assured that we are doing what is best for the American consumer with regard to the safety of dietary

supplements. In support of that effort, the Agency firmly believes that its DSSP will provide the necessary blueprint, using a phased-in approach, for a comprehensive program that will implement the additional regulatory responsibilities required of FDA by DSHEA.

FDA fully understands that it operates in a world of limited resources and competing priorities and is sensitive to the amount of resources that will be required to fully implement its DSSP. The Agency also understands the discipline required to manage and utilize these resources in the most effective and economical way possible, while at the same time achieving maximum results for the taxpayer. The Agency is committed to utilizing all resources in a manner consistent with the goals and activities delineated in DSHEA and the Strategic Plan in order to achieve success.

Mr. Chairman, there are some specific questions in your invitation letter that I did not address in my written testimony. I would be happy to respond to those or any other questions the Committee may have. Thank you.

PREPARED STATEMENT OF KAREN RUIZ, CONSUMER, SAN CLEMENTE, CA

Senator Durbin and members of the Committee,

Thank you for taking the time to both hear and read my testimony. It is my hope that by sharing with you, others will be spared from the serious and life-changing effects of taking unregulated diet supplements containing ephedra and guarana (herbal caffeine). As conditions of a legal settlement, I will not be permitted to reveal the name of the company or the names of the supplements I took.

It was February of 1996 that I used supplements containing ephedra and guarana. I was in my fifth year of marriage and had two small children. My son was just over two years of age and my daughter was six months old. I was exploring the possibilities of home-based businesses when I came across a "Moms Wanted" ad. I called the 1-800 telephone number and heard pre-recorded messages with amazing testimonials of quick weight loss, increased energy, greater physical endurance, and financial security. Still not sure what the product was, but drawn in by the claims of being "all natural", I called a second number given "for those still interested". I was referred to a local meeting that would be taking place later that evening.

While my first objective had been to find part time income, I was now interested in shedding the extra baby weight. Also, being a mom of two small children, I wanted to learn more about the extra energy the testimonials on the phone had referred to. Upon arrival, each first time guest was given a beverage sample. This was one of the more popular caffeine containing products and touted as a "healthy alternative" for coffee. By the time I left two hours later, I had heard more amazing testimonials, seen very professional videos, and listened to the head facilitator make incredible statements about this product line. I was most impressed with the claim that these products were "all natural" and that even medical doctors were unaware of the healing potential these products offered. While medical doctors push pills to fix problems, these products would work to stop the problems in the first place. The facilitator even implied some of the products could reverse major illnesses like diabetes and cancers. These statements were impressive to say the least.

The brochures I was presented with used phrases like "Doctor recommended", "scientific approach" and "quality assurance". I was very impressed with the entire presentation and found myself feeling very comfortable. At one point, I asked what ingredients were in the weight supplements that made it so effective. The response was something like this.

> "Do you ask what is in a Snickers candy bar or a McDonalds hamburger before you put it in your mouth? I could tell you the names of the ingredients but it would not mean anything to you. But I will tell you that the Chinese have been using these natural herbs for thousands of years safely." (Later I would learn that this was the answer many distributors used.)

I do wish it had been explained at this point that some of the herbs were stimulants and were responsible for the extra energy that would be felt. But the extra energy and weight loss was always attributed to the overall greater health one would achieve.

At home, my husband and I read through all the literature I had been given and didn't see anything which raised any doubts in our minds. I was excited about what I'd heard and was anxious to get started. My plan was to try these supplements for myself, then sell them if it was

all they claimed them to be. The only warning on the labels that did apply to me was that I was a nursing mother. When I inquired about the reason for this specific warning, I was told that while it was probably safe, there had been no studies done on children. With my daughter already on solid foods, she was close to being weaned anyway. So I took the next few days to stop nursing completely, and then purchased my first products from this company.

I was specifically interested in the products for weight loss and enhanced workouts. This included herbal tablets containing ma huang (the Chinese name for ephedra) and two caffeinated beverage mixes I would mix with water. With my first purchase came a brief explanation how to take them. It was also important to take them together to maximize results. Never was I given any verbal cautions, warnings, side effects to watch for, or any other clue these dietary supplements could be unsafe. How could I know that seven days later I would be in a psychiatric ward at the Anaheim Medical Center in Irvine, California?

At this point, I feel I need to make it very clear, that I had never in my life experienced any kind of mental illness. With no family member or friends having a mental illness, I did not even really know what the term referred to. I had also never done any kind of illegal substances in my youth that would have given me a reference point of being "HIGH". I believe this is why I did not stop taking the supplements when I started to experience the bizarre behavior and thought patterns. In fact, thinking I was taking the equivalent of a vitamin, I never made the connection between the product and my changing behavior.

I started the first day as directed with 1 herbal tablet in the mid-morning and 1 in the mid-afternoon. Day 2, as directed, I increased to 3 times a day, each tablet taken 45 minutes before each meal. I never did increase my dosage after that even though it was recommended to work up to 2 tablets, 3 times a day. I also began the beverage mixes according to instructions. Over the next six days, the pace of my life would speed up, and my mood would elevate to a psychotic state.

I remember feeling the lift in my energy immediately and for the first time in months I did not need to sleep while the children took their afternoon naps. In fact, it was such an amazing feeling, that I knew after the first couple days this stuff would be easy to sell. Thoughts began to flow and I became very consumed with setting up my new part time business. On day three after starting the product, I woke very early and actually went to the gym before daybreak. Then, I proceeded to go home and completely clean the house before the kids woke up. My days were full with every minute being used and I felt so productive. There seemed to be no limit to my energy. By day four, I had come up with a new marketing plan for this company and was seeking legal advice on how to patent it. In hindsight, I realize that my thoughts were becoming grandiose and irrational.

It was around day five that I began to feel something *BIG* was happening to me and I still made no connection to the product. Running on little sleep by then, I remember feeling that I was very in tune with a spiritual realm. At one point, I felt that I was being watched, and I remember being suddenly convinced that one of my neighbors was demonically possessed. Thinking she was spying on me, I shooed her out of my house when she tried to help me carry in my groceries. I was flipping in and out of paranoia, followed by what I thought were divine thoughts from God,

and I somehow became convinced I was being chosen. Initially in my psychosis, I thought I was being chosen to warn people it was the end of the world. One way I acted on these thoughts was to begin passing out twenty-dollar bills to the homeless and telling them they would be going home soon. Later, and this is embarrassing, I thought I was being chosen to be God's wife. Eventually, I just thought I was supernatural myself. There was no other explanation for feeling the way I did and knowing all that I knew (or thought I knew). To this day, I will admit it was a euphoric and incredible way to feel. As a side note, I now understand why some continue to take these ephedra-containing products even when they are informed of potential side effects. It also does not surprise me to hear that teens everywhere use these supplements as legal ways to get high.

By day five or six, my husband knew something was very wrong, but I could not be reasoned with. I was argumentative and mad whenever he tried to slow me down and discuss my behavior. I felt he was holding me back from my mission. He had called my mom and aunt to ask for help, but they too could not get through to me. My mind was racing so quickly that I could not stay focused on anything for more than seconds, and I grew more and more agitated as thoughts raced from point to point. My children were being neglected and some of the things I was saying made my husband afraid to leave them alone with me. Bottom line, you cannot reason with someone who is irrational. On the morning of the seventh day, and following more bizarre behaviors, my husband drove me to the hospital. While in the hospital, the only reason that I did not walk out was because I thought God wanted me to heal the others that were there. I was hearing voices in my head, seeing visions in the clouds, and convinced of demonic plots around me that wanted me and my family dead.

Because my husband had noticed that the change in behavior coincided with starting these supplements, he brought the products with us to the hospital. It was there that the psychiatrist assigned to me first pointed out the ephedra and guarana herbs. A prior emergency room physician, he had seen cases like me before. He explained to us that when combined, these herbs had an amphetamine effect that could lead to psychosis. We were lucky to have him given that most medical physicians are not very familiar with the herbs. Of course I could not comprehend what he was talking about at that time, but for my husband, it confirmed what he suspected. The products were to blame.

While I remained in the hospital for the next ten days, I was given strong sedating medications and had extensive counseling. The super feelings of the spiritual did begin to subside, but I was not able to give up the ideas and beliefs of who I was. I could not understand how I could have made it all up, and I believed that what I'd seen and felt while on the product was still very real. It would take two to three months before my mind would allow me to believe that all I'd experienced was a result of an amphetamine like high. Slowly, the ability to think logically did return, only to be followed by a severe and life threatening depression. From beginning to end, recovery was a nine-month process.

While I had set out to help increase our financial base, now we were completely wiped out and had outstanding medical bills. But this hardship could not compare to the emotional consequences of taking these products. My marriage was severely affected. My husband could not help but second-guess everything I said. In the episodes of depression, I would lose all

confidence and find myself unworthy of his commitment to me. I often felt he and the children would be better off with someone else. Trust and healing, for both of us, have taken years to regain. And nothing can make up for the lost time with my children. Especially since the damage has turned out to be permanent. Two years later, I would have a second episode of psychotic behavior followed by depression. And one year after that, it would happen for a third time. With each incident came fear, uncertainty, and months of medication. To stop these cycles, I now remain on a small amount of medication and have been well for almost three years. But I keep additional medications in the cupboard just in case.

Following my initial incident, we reported what had happened to my direct uplink distributors. While very concerned for me, they personally had "never seen anyone react to the product that way". There was no effort to find out details of my reaction or document it for future use. Next, we filed a lawsuit and felt lucky to have John Tiedt, an attorney who took our case on a contingency basis. Knowing me personally, he was very upset with the devastation this product had wreaked on my family. I was also determined to make a difference for future moms who would respond to that ad. It was later I would realize how many different products, containing these same controversial ingredients, were on the open market.

In his pursuit of our case, our attorney found that the labels on my products were very inaccurate. Lab tests revealed that there was more ephedra and guarana in the product than the label specified. In response to this finding, there was finger pointing between the company and the lab that actually manufactured the products for them. So each hired separate lawyers. Can you imagine the difficulty of trying to fight a case against a company with unlimited financial resources and not accountable to anyone? Their lawyers searched in vain for evidence of a pre-existing mental condition, family history of mental illness or history of drug use. There was none. But in the end, we felt we should settle. There had been no trial cases before us, and we did not have the financial capability, or endurance, to fight this giant. The money we received was just enough to cover our medical bills and replenish our small savings.

My doctors and psychiatrist have concluded one of the two following explanations.

#1. I somehow had a pre-disposition toward mental illness (which had never shown up before), and the supplements triggered its appearance.

#2. The supplements actually altered my natural brain activity and caused me to have symptoms similar to bi-polar illness.

Either conclusion is scary. Whichever way you look at it, these kinds of products are very dangerous and carry with them high risk. I have been fortunate to share my story in news clips and magazine interviews. Every single time, I receive calls from people going through the same experience. These are the lucky ones. At least they have identified the source of the problem and can discontinue use. But I worry about the victims rushed to the hospitals and mental facilities that never make the connection between starting these supplements and mental disturbances. Most patients do not think to tell their doctors they are taking "natural" supplement products. It doesn't occur to them that the supplements they are taking to achieve better health are actually causing debilitating side effects.

I know for a fact I am not alone in my experience. In addition to the people that call me, my psychiatrist sees new patients with similar symptoms regularly. With these new patients, my psychiatrist now knows to go beyond the question, "Are you taking any kind of prescription medication or illegal substances." The initial answer is usually "no", because most herb users do not think of these products as drugs, but rather as vitamin equivalents. His further questioning often reveals that the individual has been taking ephedra and guarana containing products that coincide with the on-set of mental symptoms. These include symptoms of psychosis, panic attacks, paranoia, and even schizophrenia. Each time I visit him for my check ups, his cupboards contain additional supplement products that patients have brought in. From weight loss to workout supplements, they all contain ephedra and a caffeine source.

In conclusion, I would like to mention my thoughts on what might have helped my situation. Even the improved labeling standards today would not have stopped my incident. At 26, I was healthy and had no medical concerns. I can see no other way to stop others from being hurt other than to place strict federal regulation on ephedra-containing products. With new product lines coming to the market regularly, these products continue to be advertised as "all natural" and "healthy". Since I took these supplements, similar products have now become available in grocery stores, coffee shops, gas stations, and the many health stores that have popped up around town. Never do I see posted warnings. The over the counter drug combination of synthetic ephedrine and caffeine has been banned by the FDA since the 1980's. Why is the herbal equivalent allowed on the market?

I would also recommend that the "cautions" portion of labels, nation wide, immediately be required to include the phone number of the FDA. There needs to be a place, other than the individual manufacturers, where consumers can report adverse affects. I can only hope that the money these companies donate to campaigns and supportive political leaders will not keep the issue at a stand still. The evidence of harm is abundant. How many victims will it take to finally place the burden of proof in the hands of the manufacturers? In articles I read, representatives for the industries repeatedly claim that cases like mine cannot be scientifically proven. Yet, it is the industry, which should have the requirement to prove their products are scientifically safe. Until that can be done, and the medical communities and manufacturers *both agree* on safe standards, the public should no longer be subjected to the lack of information and false claims. Please use your power of influence to make a difference.

Thank you,

Karen Ruiz

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**Wednesday, July 31, 2002**

**Subcommittee on Oversight of Government Management, Restructuring, and the District of Columbia**

**When Diets Turn Deadly: Consumer Safety and Weight Loss Supplements**

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**What is a Dietary Supplement?**

There exist three categories of chemical agents available for weight loss treatment. The first two categories are prescription drugs and over-the-counter drugs. The Federal Drug Administration (FDA) regulates these agents under carefully controlled guidelines for safety and efficacy. The process is particularly rigorous for weight loss agents as over 60% of Americans are now overweight or obese, excess adiposity effects increasing numbers of vulnerable children and adolescents, and drug treatments for weight loss have a notorious past history of both abuse and damaging physical and behavioral effects extending back over a century. Prescription and over-the-counter drugs are rigorously tested using modern scientific guidelines and procedures to ensure public and individual safety.

In 1994 a third category of agents emerged referred to as "dietary supplements". The term dietary supplements is a legal one as stated by the FDA:

*"FDA regulates dietary supplements under a different set of regulations than those covering "conventional" foods and drug products (prescription and Over-the-Counter). Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), the dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed. FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market. Generally, manufacturers do not need to register with FDA nor get FDA approval before producing or selling dietary supplements. Manufacturers must make sure that product label information is truthful and not misleading.*

*FDA's post-marketing responsibilities include monitoring safety, e.g. voluntary dietary supplement adverse event reporting, and product information, such as labeling, claims, package inserts, and accompanying literature. The Federal Trade Commission regulates dietary supplement advertising."*

Dietary supplements for weight loss, unlike traditional drugs, often include multiple ingredients; the word "supplement" is misleading as most agents do not "add" to the natural body stores of the compound nor does the agent usually prevent or correct a deficiency state.

**What Are Some of the Most Popular Weight Loss Products?**

Weight loss can be produced when ingestion or absorption of calories or energy is less than energy released from the body as heat. Dietary supplements purportedly produce weight loss by suppressing appetite, reducing absorption, increasing heat production or metabolic rate, and changing the proportion of calories stored as fat and muscle.

The ephedra alkaloids, discussed below, are thought to suppress appetite and increase energy expenditure, by two different mechanisms. These actions are enhanced with herbal sources of caffeine and aspirin are added to the ephedra-containing product.

Some agents are reported to reduce fat and thus energy absorption from the gastrointestinal tract, notably chitosan. Chitin is a substance derived from the exoskeletons (shells) of arthropods such as crabs, shrimps, and lobster.

Some dietary supplements reportedly increase the storage of ingested nutrient as muscle and decrease the proportion stored as fat. These include the herbal ingredient garcinia cambogia and the widely used group of compounds referred to as chromium picolinate and other chromium salts.

My colleagues and I have reviewed these agents in a recent report (1).

I would now like to focus some specific comments on dietary supplements that include MaHuang as the main active ingredient. I select MaHuang because consumers are exposed with these products to a potentially dangerous family of ingredients, the ephedra alkaloids, that not only produce weight loss but that may lead to strokes and heart attacks with associated disability and death in selected susceptible patients.

A key concern is that overweight and obese patients are particularly vulnerable to taking purported dietary supplement weight loss products because they are often desperate, want to lose weight quickly, find evaluations by their physicians time consuming and costly, and have often tried dietary and medical therapies of limited current effectiveness.

By avoiding medical oversight, overweight and obese consumers purchasing dietary supplements make the false assumption that dietary supplements and herbal preparations are inordinately safe and may pose no or very little risk. Moreover, many overweight and obese consumers harbor "silent" diseases such as high blood pressure and narrowing of the coronary arteries that manifest under the biological conditions produced with ingestion of the purported weight loss agent. The overweight consumer of dietary supplements who harbors a potentially silent killer may be bypassing the critical medical

oversight needed to detect, prevent, or treat a serious underlying medical condition. A large percentage of overweight and obese Americans have undiagnosed and untreated medical conditions (2).

**What is MaHuang?**

Ma-Huang, now defined as a dietary supplement in the US, is primarily used today as an ingredient in herbal weight loss products and acts to lower appetite and potentially increases energy expenditure through stimulant mechanisms (3-12).

Ma-Huang is the Chinese name of Ephedra sinica, an acrid tasting stimulant herb (1). Other Ephedra species include Ephedra equisentina and Ephedra intermedia.

**What are the Active Ingredients in MaHuang?**

The ephedra alkaloids represent a family of compounds that vary in proportion depending on plant species, harvest season, weather conditions, geographic location, and other factors. The ephedra content of dietary may vary substantially from label claims (13).

The ephedra alkaloids include the major component, up to 90%, (-)-ephedrine, up to 30% pseudoephedrine, and lesser amounts of (+/-)-norephedrine or phenylpropanolamine, and (+)-norpseudoephedrine or cathine. The +/- refers to the three dimensional positioning of atoms within the molecule and this feature of a molecule may influence its biological activity.

Ephedrine, an ephedra extract, was synthesized in 1927 and is also widely used today in weight loss and other pharmaceutical preparations, particularly in Europe. Although studies are limited, the pharmacokinetics of synthetic and botanical forms of ephedrine appear similar (14; **Appendix 1**) although some questions on drug disposition remain and more studies are needed (15). Pharmacokinetic properties of a drug describe its absorption, distribution, and elimination from the body.

Phenylpropanolamine (PPA) has biological properties similar to ephedrine and for many years was the main ingredient used in over the counter weight loss products and cough/cold preparations. A recent report supports earlier observations of increased hemorrhagic stroke risk in subjects taking PPA (**Appendix II**). The Food and Drug Administration (FDA) is taking steps to remove PPA from all drug products and has requested that drug companies discontinue marketing products containing PPA. In addition, FDA has issued a public health advisory concerning PPA. (http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3647b1_tab19.doc).

The chemical structures of ephedrine and other ephedra alkaloids are very similar to the hormones epinephrine or adrenaline and nor-epinephrine. These are the "flight and fight" hormones that have many important biological effects including increasing blood pressure, respiration, heart rate, and arousal. Ephedra alkaloids are also very similar in

structure to the banned group of chemical compounds referred to as amphetamines (**Appendix III**). Widely used five decades ago for weight loss and other stimulant effects, amphetamines were addicting and had many serious other side effects.

**How Does MaHuang Produce Weight Loss?**

Ephedrine alkaloids appear to exert their main weight loss effects by suppressing appetite and thus food intake via central "sympathomimetic" (beta-agonist) actions. Ephedrine alkaloids also appear to have a small effect on increasing energy expenditure (16). Taken collectively, the ephedra family of compounds promotes negative energy balance and weight loss by lowering both energy intake and increasing energy expenditure. Ephedrine and other Ephedra alkaloids have variable stimulant effects

Ephedrine and ephedra alkaloids alone have modest weight loss effects and their efficacy appears to be enhanced by addition of caffeine and aspirin either as the pharmaceutical grade ingredients or as their natural counterparts such as Guarana and Willow-bark, respectively (17-21).

Addition of caffeine (i.e., "Guarana") and aspirin (i.e., Willow-bark) to Ma-Huang purportedly potentiates the actions of ephedrine. Caffeine competitively antagonizes adenosine receptors and may be an adrenaline antagonist; adenosine is a hormone produced by endothelial cells that dilates blood vessels. Many commercial weight loss preparations include varying proportions of these three components. Caffeine per se has a small thermogenic (i.e., heat-producing) effect in humans (17). Aspirin has actions that also potentiate ephedrine actions.

**Is MaHuang Effective as a Weight Loss Agent?**

There are many studies that have examined the effectiveness of ephedrine alone or in combination with other ingredients; fewer studies examine the weight loss effects of ephedra alkaloids in combination with other natural sources of caffeine and aspirin.

The collective studies strongly support the premise that ephedrine, particularly in combination with caffeine and also aspirin, promote significant short-term (~3-6 months) weight loss when ingested as part of an intervention program including dietary and lifestyle management. Long-term (>6 months) controlled trials with large and diverse subject populations are lacking.

The efficacy of Ma-Huang, separate from that of chemically synthesized ephedrine, is supported by fewer published abstracts and papers, although conceptually, there is no reason to expect a "large" difference between "natural" ephedra and chemically-synthesized ephedrine. As noted earlier, the pharmacokinetics of chemically synthesized and botanical sources of ephedrine appear similar (**Appendix I**).

A major limitation of reviewed research is that most studies administered ephedrine or Ma-Huang in forms that mimic commercially available preparations and thus: the

efficacy of ephedrine as a sole weight loss agent is not entirely clear and is questionable; the efficacy of ephedrine with varying amounts of caffeine and aspirin is difficult to ascertain as studies failed to include varying amounts of these other agents independent of ephedrine or as separate experimental limbs in controlled trials.

Ephedrine is used in association with caffeine and aspirin, or their herbal equivalents guarana and willow bark, to produce the "fat-burning stack (18)." The stack has some evidence to support its efficacy and is used in Europe. The three compounds, when taken in the following ratio, 200 mg caffeine/60mg epihedrine/300mg aspirin, produces a significant thermogenic effect. Very limited published information is available on the safety and efficacy of the "stack" or related products.

A concern is that the concentration of ephedrine in the plant and method of preparation vary widely among products (13). Product labels may therefore not reflect actual ingredient content or bioavailability.

**Are Ephedra-Containing Products Safe?**

Why do we know that ephedra alkaloids may be unsafe in some consumers? Scientists know that ephedra alkaloids, particular when used in combination with potentiating agents that include caffeine and aspirin, produce variable increases in blood pressure, heart rate, cardiac output, and respiration (**Table 1**). These effects in susceptible individuals can trigger heart attacks and strokes.

The molecular basis of the stimulant effect for the class of compounds, "sympathomimetic agents", is well known. While the effects of ephedra alkaloids alone or in combination are often small in magnitude and transient, given the large and potentially medically vulnerable obese population taking these agents we can predict that some individuals with have a relatively large drug-induced biological effect. Others may have only a small effect but be medically vulnerable due to silent underlying heart or cerebrovascular diseases. Many of the patients taking these agents do so in the complete absence of medical supervision or evaluation. They may inadvertently take a large dose due to product variation or consciously in the hope of boosting their weight loss. Unsupervised, they may unduly exercise or take excessive amounts of caffeinated beverages or aspirin. The predictable result, given the millions of Americans taking these products, is serious medical events including heart attacks and strokes.

Given the well-recognized risks of this group of dietary supplements and the appropriate lack of interest in the area by pharmaceutical companies, there exist very few careful safety and efficacy trials that meet the current standards set forth for evaluation of pharmaceutical weight loss agents.

In the studies carried out by my colleagues and I using a commercial weight loss product containing ephedra and caffeine as active ingredients, some patients in the "active" treatment group experienced untoward effects at "usual" doses such as palpitations, blood pressure elevations, and other typical stimulant effects that led to their discontinuation in

the study (21). I have observed similar effects in other unpublished ephedra studies carried out at our institution. These effects are the well characterized sympathomimetic effects that I mentioned earlier and that support our projection that some medically unscreened patients with underlying disease may suffer heart attacks and strokes following ingestion of this or similar dietary supplements. This projection is supported by the study of Haller and Benowitz (23)(**Appendix IV**).

Another concern with the few well controlled trials is that subjects were appropriately medically screened prior to entry into the trial so as to reduce the medical risks of those exposed. One such trial was carried out at our institution (22) and only those subjects deemed medically acceptable were entered into treatment. Rigorous testing of blood pressure and heart rhythm was used to detect and eliminate those subjects who may have suffered a serious adverse event during the trial. The lack of serious injuries and side effects in trials such as these cannot be interpreted as a safety endorsement as the actual consumer population still includes the medically vulnerable and unscreened individual who may harbor a potentially lethal silent disease manifest by ingestion of ephedra alkaloids.

Specifically, concerns have been raised about the safety of products containing Ma-Huang/ephedra. Several serious case-reports of adverse effects and fatalities have appeared in the literature. Strokes, myocardial infarction, and cardiac arrhythmias are reported in association with ephedra ingestion. Benowitz and Haller (23; **Appendix IV**) provided the FDA with an independent review of adverse events related to ephedra alkaloid containing supplements. The authors concluded that ephedra alkaloids may pose a health risk for selected individuals. Some of the reported side effects in patients occurred within the commonly used therapeutic ranges.

Ephedrine alone or combination with other ingredients may raise heart rate and blood pressure (e.g., systolic BP increase ~3-7 mmHg) in some subjects (1-23), although the magnitude and length of time for which these adverse effects remain evident is not well established. Restlessness, headache, and insomnia have been reported by subjects ingesting some commercial dietary supplements and with ephedrine-caffeine combinations. Subjects with bleeding tendencies may be at risk when taking aspirin-like compounds.

Taken collectively, Ma-Huang taken alone or combination with other agents may place certain subjects at risk of adverse and potentially fatal effects. More long-term safety data, beyond six months, is needed, particularly in selected populations such as the elderly.

Finally, there exists particularly vulnerable populations such as pregnant or lactating women, the elderly, and subjects with eating disorders in whom particular concern exists for their use of weight loss dietary supplements.

**Should the Regulations for Dietary Supplements be Changed?**

Although my review here has been brief and focused, we can envision two types of dietary supplement for weight loss: one that is safe and ineffective and the other that is effective but unsafe.

The first type of product provides false hope to the unwitting highly vulnerable overweight or obese consumer and delays their entry into an appropriate medical or nutritional care system.

The second type of product is more dangerous and actual product efficacy will lure consumers into trying the product while erroneously assuming dietary supplements, because of their herbal or natural ingredients are unduly safe compared to their pharmaceutical counterparts.

Improved product safety testing, quality control, labeling, and nomenclature are all needed in order to forestall or eliminate the problems now inherent with the dietary supplement category of weight loss products.

**Table 1**. Patterns of Signs and Symptoms Associated With Dietary Supplements Containing Ephedrine Alkaloids.[1]

| ORGAN/SYSTEM INVOLVED | CLINICAL SIGNIFICANCE | SIGNS AND SYMPTOMS |
|---|---|---|
| Cardiovascular system | Serious | Dysrhythmias, severe hypertension, cardiac arrest, angina, myocardial, infarction, and stroke[2] |
| | Less clinically significant | Tachycardia, mild hypertension, palpitations. |
| Nervous system | Serious. | Psychosis, suicidal, altered or loss of consciousness (including disorientation or confusion), and seizures. |
| | Less clinically significant | Anxiety, nervousness, tremor, hyperactivity, insomnia, altered behavior, memory changes. |
| Gastrointestinal (GI) | Serious | Altered serum enzymes, hepatitis. |
| | Less clinically significant | GI distress (nausea, vomiting, diarrhea, constipation). |
| Dermatologic | Serious | Exfoliative dermatitis |
| | Less clinically significant | Less clinically significant Nonspecific rashes. |
| General manifestations | | Numbness, tingling, dizziness, fatigue, lethargy, weakness. |

[1] Reproduced from Federal Register: June 4, 1997 (Volume 62, Number 107), Dietary Supplements Containing Ephedrine Alkaloids.

[2] For the purposes of this document, strokes (i.e., cerebrovascular accidents) are considered to be related to the cardiovascular system, because predisposing or inciting factors include hypertension, dysrhythmias and ischemia, although it is recognized that the consequences affect the central nervous system.

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## Appendix I

### Pharmacology of ephedra alkaloids and caffeine after single-dose dietary supplement use.

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OBJECTIVE: Serious cardiovascular toxicity has been reported in people taking dietary supplements that contain ma huang (Ephedra) and guarana (caffeine). We assessed the pharmacokinetics and pharmacodynamics of a dietary supplement that contains these herbal stimulants. METHODS: Eight healthy adults received a single oral dose of a thermogenic dietary supplement labeled to contain 20 mg ephedrine alkaloids and 200 mg caffeine after an overnight fast. Serial plasma and urine samples were analyzed by use of liquid chromatography-tandem mass spectrometry for ephedrine alkaloid and caffeine concentrations, and heart rate and blood pressure were monitored for 14 hours. RESULTS: Plasma clearance and elimination half-lives for ephedrine, pseudoephedrine, and caffeine were comparable to published values reported for drug formulations. A prolonged half-life of ephedrine and pseudoephedrine was observed in 1 subject with the highest urine pH. Mean systolic blood pressure increased significantly to a maximum of 14 mm Hg above baseline at 90 minutes after ingestion ($P < .001$). There was a lag in the mean heart rate response that reached a maximum change of 15 beats/min above baseline at 6 hours after ingestion ($P < .001$). Diastolic blood pressure changes were insignificant. Two subjects who were taking oral contraceptives had longer caffeine half-lives (15.5 +/- 0.3 hours versus 5.6 +/- 1.7 hours) and lower values for oral clearance (0.34 +/- 0.01 mL/min. kg versus 0.99 +/- 0.41 mL/min. kg) than subjects who were not taking oral contraceptives. CONCLUSIONS: Botanical stimulants have disposition characteristics similar to their pharmaceutical counterparts, and they can produce significant cardiovascular responses after a single dose.

**Appendix II**

PHENYLPROPANOLAMINE & RISK OF HEMORRHAGIC STROKE:
Final Report of The Hemorrhagic Stroke Project

## May 10, 2000

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On Behalf of the HSP Investigators

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**EXECUTIVE SUMMARY**

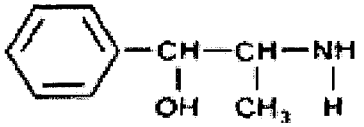
Case reports have linked exposure to phenylpropanolamine (PPA) to the occurrence of hemorrhagic stroke. Many of the affected patients have been young women using PPA as an appetite suppressant, often after a first dose. To further examine the association between PPA and c, we designed a case-control study involving men and women ages 18 to 49 years who were hospitalized with a subarachnoid hemorrhage (SAH) or intracerebral hemorrhage (ICH). Eligible case subjects had no prior history of stroke and were able to participate in an interview within 30 days of their event. Case subjects were recruited from hospitals in four geographic regions of the United States. For each case subject, random digit dialing was used to identify two control subjects who were matched on age, gender, race, and telephone exchange. Cases and control subjects were interviewed to ascertain their medical history, health behaviors, and medication usage. A subject was classified as exposed to PPA if they reported use within 3 days of the stroke event for case subjects or a corresponding date for control subjects, and the exposure was verified.

The final study cohort comprised 702 case subjects and 1376 control subjects. All control subjects were matched to their case subjects on gender and telephone exchange. Age matching was successful for 1367 controls (99%) and ethnicity matching was achieved for 1321 controls (96%). For the association between hemorrhagic stroke and any use of PPA within three days, the adjusted odds ratio was 1.49 (lower limit of the one-sided 95% confidence interval (LCL)=0.93, p=0.084). For the association between hemorrhagic stroke and PPA use in cough-cold remedies within the three-day exposure window, the adjusted odds ratio was 1.23 (LCL=0.75, p=0.245). For the association between hemorrhagic stroke and PPA use in appetite suppressants within the three-day exposure window, the adjusted odds ratio was 15.92 (LCL=2.04, p=0.013). For the association between PPA in appetite suppressants and risk for hemorrhagic stroke among women, the adjusted odds ratio was 16.58 (LCL=2.22, p=0.011). For first dose PPA uses among women, the adjusted odds ratio was 3.13 (LCL= 1.05, p = 0.042). All first dose PPA use involved cough-cold remedies.

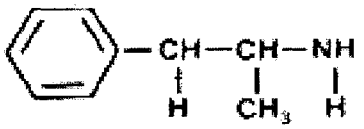
In conclusion, the results of the HSP suggest that PPA increases the risk for hemorrhagic stroke. For both individuals considering use of PPA and for policy makers, the HSP provides important data for a contemporary assessment of risks associated with the use of PPA.

**Appendix III**

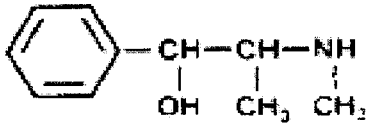
**PHENYLPROPANOLAMINE**



**AMPHETAMINE**



**EPHEDRINE**



**Appendix IV**

## Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids.

Haller CA, Benowitz NL.

Department of Medicine, University of California, San Francisco, and the California Poison Control System, 94143-1220, USA.

BACKGROUND: Dietary supplements that contain ephedra alkaloids (sometimes called ma huang) are widely promoted and used in the United States as a means of losing weight and increasing energy. In the light of recently reported adverse events related to use of these products, the Food and Drug Administration (FDA) has proposed limits on the dose and duration of use of such supplements. The FDA requested an independent review of reports of adverse events related to the use of supplements that contained ephedra alkaloids to assess causation and to estimate the level of risk the use of these supplements poses to consumers. METHODS: We reviewed 140 reports of adverse events related to the use of dietary supplements containing ephedra alkaloids that were submitted to the FDA between June 1, 1997, and March 31, 1999. A standardized rating system for assessing causation was applied to each adverse event. RESULTS: Thirty-one percent of cases were considered to be definitely or probably related to the use of supplements containing ephedra alkaloids, and 31 percent were deemed to be possibly related. Among the adverse events that were deemed definitely, probably, or possibly related to the use of supplements containing ephedra alkaloids, 47 percent involved cardiovascular symptoms and 18 percent involved the central nervous system. Hypertension was the single most frequent adverse effect (17 reports), followed by palpitations, tachycardia, or both (13); stroke (10); and seizures (7). Ten events resulted in death, and 13 events produced permanent disability, representing 26 percent of the definite, probable, and possible cases. CONCLUSIONS: The use of dietary supplements that contain ephedra alkaloids may pose a health risk to some persons. These findings indicate the need for a better understanding of individual susceptibility to the adverse effects of such dietary supplements.

# UNITED STATES OF AMERICA

## BEFORE THE SUBCOMMITTEE ON OVERSIGHT OF GOVERNMENT MANAGEMENT, RESTRUCTURING AND THE DISTRICT OF COLUMBIA

### UNITED STATES SENATE

**Testimony of Michael McGuffin**
**President**
**American Herbal Products Association**

July 31, 2002

My name is Michael McGuffin. I am president of the American Herbal Products Association (AHPA), the national trade association and voice of the herbal products industry. AHPA serves its members by promoting the responsible commerce of products which contain herbs and which are marketed as dietary supplements and are used to enhance health and quality of life. I have been associated with the herbal products industry for over twenty years and was an owner and manager of an herbal product company prior to taking my present position. I am pleased to respond on behalf of AHPA to the questions posed by the Subcommittee.

**How does the supplement industry self-regulate and keep potentially dangerous, ineffective, or contaminated supplements from being sold to consumers?**

As the Subcommittee is aware, it is a crime under the Federal Food, Drug and Cosmetic Act to sell an adulterated (contaminated or dangerous) or misbranded (falsely or misleadingly labeled) dietary supplement. In addition, the Food and Drug Administration and the Secretary of Health and Human Services have the power to regulate potentially dangerous dietary supplements and to proceed summarily against dietary supplements that pose an imminent hazard for consumers. The Federal Trade Commission, acting under the Federal Trade Commission Act, also acts against dietary supplements that are advertised falsely, or that make misleading claims or are otherwise not unfair or deceptive. Most states have laws that track these federal laws.

AHPA and its members have been and continue to be actively involved in self-regulatory activities related to dietary supplements containing herbal ingredients. One of the ways that AHPA promotes responsible commerce in herbal dietary supplements is by establishing trade recommendations for its members. These self-regulatory policies are defined as conditions of membership and are set forth in AHPA *Code of Ethics &*

*Business Conduct*, attached hereto and should be considered as part of our response to this question. We also inform the FDA and the FTC of our policies.

Several of AHPA's trade recommendations are responsive to the issues identified in this question. Thus, in 1996 a trade recommendation was adopted to require that products containing herbs with toxic pyrrolizidine alkaloids, such as comfrey, be labeled for limited and external use only. FTC initiated enforcement against a company two years ago on grounds significantly similar to AHPA's trade recommendation on comfrey. Similarly, two policies have been adopted, one in 1997 and one in 2001, to prevent the internal use of plants that contain aristolochic acid, which is potentially nephrotoxic and carcinogenic. FDA initiated a series of product recalls in 2001 on grounds significantly similar to AHPA's policy on aristolochic acid. AHPA has also adopted specific responsible labeling recommendations for chaparral (January 1995), and kava (Sept. 1997 and revised). With respect to herbal ingredients used for weight loss, AHPA has established trade recommendations for ephedra (March 1994 and revisions) and stimulant laxatives (July 1995 and revised).

AHPA also published the *Botanical Safety Handbook* in 1997 to provide safety information for over 500 botanicals, including most of those widely sold in United States commerce. The information contained in this document is useful in providing manufacturers with information that can assist in the labeling of herbal products, and our organization has adopted a policy that will require the use of such labeling beginning in October of this year. In at least one case, FDA has utilized the recommendations in this AHPA reference to support regulatory action taken with respect to herbal product labeling.

AHPA has no monitoring or enforcement mechanism for the trade recommendations that have been adopted by our Board of Trustees on our members' behalf. We have, however, turned away prospective members who were not in compliance on at least two occasions. We firmly believe all of our self-regulatory trade recommendations and guidelines are in the public interest and promote responsible commerce in botanicals. We also believe that we have been and remain ahead of federal regulatory agencies with respect to encouraging the herbal supplement industry to label their products with useful and important information for consumers.

With regard to the issue of product contamination, AHPA was one of several trade associations who submitted a proposal to FDA for the establishment of current good manufacturing practice (cGMP) for dietary supplements in 1995. Dietary supplements are currently regulated under cGMP for foods as found in Title 21 of the *Code of Federal Regulations*, Part 110. The state and federal laws I mentioned at the outset already forbid the introduction into commerce of contaminated foods and cGMP regulations establish the appropriate practices for their manufacture. Nevertheless, AHPA believes that cGMP specific to dietary supplements may provide better protection against contamination.

AHPA is aware that other trade organizations are also engaged in activities related to the safe use of uncontaminated dietary supplement that effectively provide benefits for consumers. The National Nutritional Foods Association (NNFA), for example, has produced a number of background documents on key dietary ingredients. In addition, NNFA has established a cGMP audit program for dietary supplement manufacturers. Also, the Council for Responsible Nutrition (CRN) has published documents related to the safety and utility of numerous nutritional supplements. Both associations were part of the group that established the draft cGMP for dietary supplements in 1995.

**What types of training, experience, and certification are required to become a dietary supplement manufacturer?**

The FDA's cGMP for foods requires that manufacturers of foods, and so by extension dietary supplements, assure that personnel responsible for identifying sanitation failures or food contamination have education and/or experience to provide a level of competency necessary for production of clean and safe food. In addition, this regulation requires food and dietary supplement handlers and supervisors to receive appropriate training in proper food handling techniques and food-protection principles and to be informed of the danger of poor personal hygiene and unsanitary practices.

When AHPA and others submitted our proposed cGMP for dietary supplements to FDA in 1995, we suggested that the requisite training and experience for manufacturing dietary supplements be extended beyond the basic sanitary concerns identified for foods. Thus, we requested that FDA establish a requirement that **all** persons engaged in the manufacture of a dietary supplement product, not only those responsible for sanitation, should have the proper education, training, and experience (or any combination thereof) needed to perform the assigned functions. We also proposed that all training should be in the particular operation(s) that the employee performs as they relate to the employee's functions and that appropriate documentation of training be retained by the manufacturer.

The industry proposal for cGMP for dietary supplements was published by FDA as an advance notice of proposed rulemaking in the *Federal Register* on February 6, 1997. Although completion of this process has been listed as an agency priority in each of the past several years, no subsequent publication of a proposed rule for dietary supplement cGMP has been forthcoming in the intervening 5 years.

***To the best of AHPA's knowledge, there are no certification requirements to become a manufacturer of a food, drug, or a medical device.*** Somewhat similar to the cGMP for foods but more like the cGMP proposed by dietary supplements for industry, the FDA cGMPs for these other product categories require that persons engaged in the manufacture these products must be have experience or training for their particular position.

**Can you describe specific efforts the industry has made to deal with companies or individuals promoting ineffective or unsafe products?**

As stated at the outset, it is a crime to market an adulterated or misbranded dietary supplement. The FDA through the Department of Justice and the FTC have authority to enforce these laws, whereas industry has no such authority. Specific efforts that the industry has made to deal with products that are not in conformity with existing laws involve communication with one or another of these enforcement agencies.

For example, FDA issued a press release in April 1996 to warn consumers regarding companies who were engaged in plainly unlawful labeling products as dietary supplements that were being marketed and sold as substitutes for illegal drugs. We subsequently submitted comments to a meeting of the Special Working Group on Foods Containing Ephedrine Alkaloids of the FDA's Food Advisory Committee on August 27, 1996 in which we suggested that such products were illegal and subject to federal enforcement under the Controlled Substances Analogue Enforcement Act of 1986. Some limited enforcement occurred about a year later, in August 1997, but it was not until almost four years later, in April 2000, that FDA actually issued guidance in this matter. Frankly, FDA's limited response with respect to what have come to be called "street-drug knockoffs" was surprising given this government's firmly established policies against substance abuse.

Another example is the action that AHPA initiated last fall when our country was dealing with the fear generated by letters delivered to U.S. Senate offices and elsewhere that contained potentially deadly anthrax spores. Within a matter of weeks of these terrorist attacks, AHPA developed a policy against the sale or marketing of any dietary supplement for treatment or prevention of anthrax. We communicated this position not only to the FDA and to the FTC but also to several organizations that represent practitioners of various disciplines of complementary and alternative therapies. Many of these organizations followed AHPA's lead in this matter, and FTC also made it clear that it would not tolerate advertising either supplements or medical devices for such a purpose.

With respect to ephedra, AHPA actively communicated its labeling recommendation for ephedra-containing dietary supplements in the spring of 1994, even before the Dietary Supplement Health and Education Act of 1994 was passed. FDA initiated an Ephedra product labeling rulemaking in 1997 and that proposal has since been essentially withdrawn. Because labeling is important, AHPA and the other trade associations of the dietary supplement industry filed a Citizen Petition with the FDA in October 2000 that would have had FDA adopt an enforcement policy essentially mandating ephedra product labeling. FDA's response has been that the proposal raises complex issues and will take a substantial time to address.

There is a limit, however, to what any trade association can do to separate out bad products or bad actors. Rather, in our system we rely on the "big stick" of the federal enforcement agencies. AHPA and other trade associations have expressed their support for Congressional appropriation of sufficient funds specifically earmarked for dietary supplement enforcement by FDA. There was an increase in such funding for the current

fiscal year, and I am sure that the industry, consumers and Congress should see heightened FDA enforcement.

**Can you tell us about Dr. Bill Gurley's 2000 study, in the American Journal of Health-System Pharmacy, on the high rate of variability in the quantity of active ingredients seen in ephedra-containing products?**

AHPA issued a press release on May 19, 2000 that examined Dr. Gurley's article, especially in relation to products that he tested that were manufactured by AHPA member companies. A copy of that press release is attached hereto and should be incorporated into this response.

**What safeguards has the industry established to ensure that the quantities included in a supplement product match the quantities listed on the label?**

It is a crime to label a product as containing ingredients or amounts of ingredients that are not in the product. That has been the law since 1906.

As discussed above, the dietary supplement industry submitted a proposal for cGMP regulations to FDA in 1995. Some elements of this industry proposal were designed to assure that the identity and quantity of ingredients added to dietary supplements are accurate when they are manufactured. Botanical ingredients in dietary supplements present unique analytical challenges for companies that choose to identify and quantify an herb's constituents on their product's label. Several companies have therefore provided funding for the past several years to support nonprofit organizations such as the American Herbal Pharmacopoeia (AHP) and the Institute for Nutraceutical Advancement (INA). These organizations have published quality monographs and analytical methods for a number of botanicals (AHP) and have developed such methods for other herbs and non-herbal ingredients (INA). More recently, AOAC International has become actively involved in the process of validating these and other analytical methods.

The validation of analytical methods is an expensive process as it involves the efforts of multiple qualified analytical laboratories in the simultaneous review of a target method. Often this is done on a voluntary basis, producing inevitable delays in the process. In order to accelerate this important work, AHPA communicated actively with the U.S. Senate's Committee on Appropriations to recommend funding to support this work. Our efforts were ultimately successful, resulting in appropriations through the National Institute of Health's Office of Dietary Supplements in the current fiscal year. These funds are earmarked for the development of additional analytical methods for ingredients in dietary supplements.

**What safeguards does the industry have to ensure that contamination doesn't occur as just recently happened with the product Nettle, by Nature's Way Products, which was found to be contaminated with high amounts of lead?**

Contamination or adulteration of products occurs in all of the FDA regulated industries. The FDA urges companies to report such situations to the agency when they find adulteration or when it is brought to their attention. Nature's Way acted responsibly by reporting to FDA and conducting a recall. Their response was similar to that taken by ConAgra with the announcement last week of the recall of 19 million pounds of beef potentially contaminated by pathogens.

FDA's website (www.fda.gov/oc/po/firmrecalls/archive.html) maintains records of all recalls conducted for products that it regulates. A review of all such records from January 1, 2002 records 39 incidents of food recalls, usually for undeclared ingredients or pathogenic contamination. In addition, four drugs have been recalled in 2002, as have two medical devices, one feed supplement and one infant formula. Besides the Nature's Way product there has been one other recall of a dietary supplement this year.

AHPA has adopted two trade recommendations that deal directly with adulteration of herbal dietary ingredients. In 1997, AHPA adopted a policy to recommend that appropriate steps be taken to assure that four specifically identified herbs are not inadvertently confused with known potential adulterants. AHPA has developed a proposal to provide better information to manufacturers to assist in this process. In addition, AHPA issued a trade recommendation in 1999 related to the potential presence of pesticides in ginseng. This trade recommendation was issued after our industry became aware that ginseng growers and shippers in the Far East were using pesticides in the growing and storing of ginseng. Industry representatives met with source country regulatory authorities and expressed concern over the situation. FDA was kept fully apprised of our efforts in this regard and in fact detained a number of ginseng shipments coming into the United States.

It is our intention to address the issue of heavy metals in botanicals in a similar fashion. In this regard, we are working to develop a comprehensive testing program that will include testing of botanical raw materials prior to their shipment to the United States. In addition, we intend to work with our supplier members and with the governments of supplier countries to assure that this problem is addressed at it source.

**How do members of your organization handle adverse event reports?**

Based on conversations with several AHPA members in preparation for this hearing, it appears as if most marketers of dietary supplements are prepared to receive calls from their customers who may have complaints, including adverse event reports. Some companies employ staff or consultants who are health professionals to handle all calls that are identified as adverse event reports. Others employ staff who the company judges to be qualified by training or experience to handle such calls.

One of the elements of the proposed cGMP for dietary supplements submitted to FDA in 1995 included a requirement for the retention and follow-up on consumer complaints, including complaints of adverse events.

**What is the industry's position on registration of supplement manufacturers and distributors?**

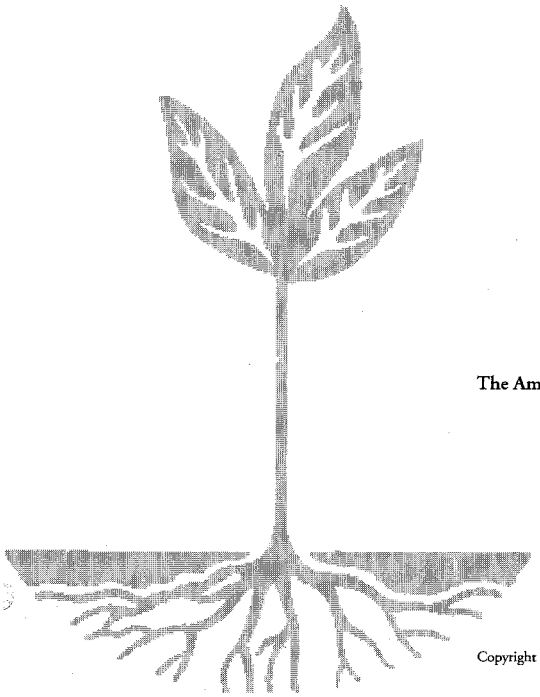
The Public Health Security and Bioterrorism Preparedness and Response Act was signed into law by President Bush on June 12, 2002. This law amended the Federal Food, Drug and Cosmetic Act by requiring that any facility engaged in manufacturing, processing, packing or holding food for consumption in the United States be registered with the Secretary of Health and Human Services (HHS). This new statutory requirement will take effect not later than 18 months after the passage of this law and will apply to any facility engaged in manufacturing, processing, packing or holding dietary supplements for consumption in the United States. This is because dietary supplements are regulated in the main as foods. I will have attended a meeting at FDA on July 30, 2002 where the food and dietary supplement industry were briefed on FDA's plans to implement this law.

It is AHPA's position and the industry's position generally that companies engaged in the dietary supplement industry should be in conformity with all federal, state and local laws. In order to assist in this process, AHPA informed its members on June 17, 2002 of the passage of the new law and will continue to actively communicate with industry and the relevant regulatory agencies to assure wide conformity with facility registration rules.

AMERICAN HERBAL PRODUCTS ASSOCIATION

# *Code of Ethics*
# & Business Conduct

*June, 2002*



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# Preface

The American Herbal Products Association (AHPA) was founded in 1983 by a group of companies active in the trade of botanicals. AHPA is now the national trade association and voice of the herbal products industry, comprised of domestic and foreign companies doing business as importers, growers, processors, manufacturers, marketers, and distributors of herbs and herbal products.

AHPA exists to promote the economic health of the herbal products industry and to help make high quality herbal products available to consumers. The Association serves its members by promoting the responsible commerce of products that contain herbs and that are used to enhance health and quality of life.

AHPA originally adopted its *Code of Ethics & Business Conduct* in 1991. Members of the Association are required to sign a statement of compliance with the *Code* and to adhere to all of its policies and principles. In their voluntary endorsement of these meaningful guidelines, AHPA members support the promotion of industry self-regulation. Responsible commerce is best assured by the adoption of policies that are developed from experience and knowledge, and the self-regulatory model relies on the experience of the governed industry.

One of the central tenets of AHPA's *Code* is its flexibility. As stated in this document, the *Code* can be revised either by the issuance of a trade recommendation by the Association's elected Board of Trustees, or by action of the membership. While the latter mechanism is rarely used, the Board has actively pursued the adoption of specific trade recommendations that serve to provide specific guidance for the herbal industry.

This *Code of Ethics & Business Conduct* reflects the ethics of the American Herbal Products Association, as determined by action of its members. Only an active and supportive membership, one that shares a commitment to responsible trade in quality herbal products, can give real meaning to the words contained here and make this document reflective of a vital and growing herbal industry.

# Contents

# Expectations of Members

## in Good Standing of the Association

### Conformity

• Members must conform to the *Bylaws, Code of Ethics & Business Conduct*, and any other policies and regulations of the Association.

• Members must conform to all the regulatory requirements of their respective federal, state and local governments.

### Fair and Honest Business

• All business transactions should be conducted in a fair and truthful manner, including all dealings with vendors and customers.

• Members will not engage in false or misleading advertising. Members may identify themselves as an AHPA member in advertising and marketing materials. However, Association involvement should not be used for personal or partisan gain. Members may not infer AHPA endorsement of any of their products.

• Members should never discuss or exchange information related to the following areas as they are generally recognized as unlawful or in violation of anti-trust laws:

1. prices or pricing
2. credit terms, discounts or elements of the terms and condition of sale
3. profit levels, costs or market shares
4. boycotts or agreements not to deal with competitors, customers or suppliers
5. allocation or division of markets or customers

• Members should conduct themselves in a professional manner with all competitors and regulatory agencies.

• When the business conduct of any member becomes prejudicial to the character and welfare of the Association, or if any member exhibits conduct in any way contrary to or in violation of this *Code* or the Association *Bylaws*, such conduct will be referred to the Board of Trustees for its action under Article IV, Section 7 of the *Bylaws*, entitled "Suspension, Expulsion and Reinstatement of Membership."

### Specific Guidelines for Herbal Products

Members must follow all Board of Trustee trade recommendations with regard to specific herbal products (these are outlined in detail in the section entitled "Current Trade Recommendations") as they are issued from time to time.

## Endangered Species (revised September 2000)

Endangered species of plants should not be traded by AHPA members. Members who wish to use such species in their products should obtain them from verifiable, commercially cultivated sources. Members should encourage selective harvesting and stewardship of wild stands of plants to maintain viable local plant populations.

- The term "endangered species" is consistent with the definitions of endangered species as established by the U.S. Endangered Species Act or as established by CITES Appendix I.
- AHPA members who use plants listed in CITES Appendix II are encouraged to do so in a manner consistent with the spirit and letter of CITES Appendix II.

## Cooperative Efforts

Members are encouraged to fund and work cooperatively on industry-wide trade issues.

# How to Amend the *Code*

The *Code of Ethics & Business Conduct* may, at times, need to be amended. There are two ways to amend the *Code*.

1. The Board of Trustees may issue a trade recommendation which becomes an amendment to the *Code*. This is done without consultation or vote by the membership of the Association.
2. Any AHPA member in good standing or an AHPA Committee may submit proposed amendments to the AHPA Board of Trustees for approval by majority vote of the Board of Trustees at the next duly constituted meeting of the Board. Upon approval by the Board, the amendment, along with a proposed effective date, in the event of approval by the membership under the terms of this section, shall be distributed to all voting members not less than 30 days before the date established by the Board for a vote by membership. Members will have no fewer than 30 days to cast their vote. Voting may occur either at a duly constituted meeting of the members, in which case a majority vote is required, or by written vote in compliance with the Article V of the *Bylaws*.

Any changes to the *Code* will be communicated to the members in writing.

# Current Trade Recommendations

## of the American Herbal Products Association

The *Bylaws* of the American Herbal Products Association as revised in January, 1998 define "Obligations of Membership" to include "adherence to all policies and business practices as outlined in the *Code of Ethics*." The *Code of Ethics*, as amended in 1996, establishes a procedure whereby "The Board of Trustees may issue a trade recommendation which becomes an amendment to the *Code*." Any recommendation of the Board is thus automatically considered as a revision to the *Code*, requiring compliance from all members in good standing. The current trade recommendations are listed on the following pages.

### I. Lady's Slipper (adopted July 1988; revised November 1999)

Whereas the roots of Lady's Slipper, *Cypripedium* spp. (notably *C. acaule* and *C. parviflorum*) have historically been traded as wild botanicals and, given the recognition of the threatened status of these and other orchids (resulting from extirpation for commercial purposes and other causes); AHPA hereby encourages and requests its members and all other businesses and individuals in the horticultural and herb trade to refrain from trade in wild-harvested Lady's Slippers. AHPA further encourages its members and others in the herb trade to support research in ecology, demographics, cultural methods, plus sexual and asexual propagation of *Cypripedium* species.

### II. *Herbs of Commerce* (adopted 1992; revised November 1999)

AHPA recommends the use of the standard common names listed in *Herbs of Commerce* (1992) to comply with the Federal labeling requirements for identification of ingredients in foods and in dietary supplements, as such requirements are specified in 21 CFR §101.4(a)1 and 21 CFR §101.4(h).

### III. Ephedra (adopted March 1994; revised March 2001)

AHPA recommends the following criteria for marketing of dietary supplement products containing ephedrine alkaloids:

#### *Labeling*

(i.) The label of the goods should bear an adequate cautionary statement, which shall at a minimum include the following language, or comparable language:

*WARNING. Not intended for use by anyone under the age of 18. Do not use this product if you are pregnant or nursing. Consult a health care professional before using this product if you have heart disease, thyroid disease, diabetes, high blood pressure, depression or other psychiatric*

*conditions, glaucoma, difficulty in urinating, prostate enlargement, or seizure disorder, if you are using a monoamine oxidase inhibitor (MAOI) or any other prescription drug, or you are using an over-the-counter drug containing ephedrine, pseudoephedrine or phenylpropanolamine (ingredients found in certain allergy, asthma, cough/cold and weight control products).*

*Exceeding recommended serving will not improve results and may cause serious adverse health effects.*

*Discontinue use and call a health care professional immediately if you experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms.*

*(ii.)* The product label shall list the amount of ephedrine alkaloids and caffeine alkaloids, if present, per serving.

### *Serving Limits*

Products are not to contain in excess of 25 milligrams (mg) of total ephedrine alkaloids per serving; usage instructions should limit daily consumption to 100 mg of total ephedrine alkaloids.

### Herbs of Commerce *Conformity*

Label identification must be in conformity with the standard common name listed in *Herbs of Commerce.*

### *Synthetic Ingredients*

Neither finished consumer goods nor raw materials used in their manufacture are to contain any synthetically derived ephedrine alkaloids or their salts (e.g., ephedrine sulfate; pseudoephedrine hydrochloride; phenylpropanolamine hydrochloride).

### *Marketing*

No claims shall be made that the product may be useful to achieve an altered state of consciousness, euphoria, or as a "legal" alternative for an illicit drug.

## IV. Chaparral (adopted January 1995)

In the interest of consumer education and well being, AHPA recommends that, if member companies choose to sell chaparral (*Larrea tridentata*), all consumer labeling contain the following informational language, as well as the phone number shown below for reporting unusual conditions associated with the ingestion of chaparral:

*Seek advice from a health care practitioner before use if you have had, or may have had, liver disease. Discontinue use if nausea, fever, fatigue or jaundice (e.g., dark urine, yellow discoloration of the eyes) should occur. (To report unusual conditions, call (301) 588-1171).*

## V. Stimulant Laxatives (adopted July 1995; revised March 2001)

With the exception of those products containing senna, cascara sagrada, or aloe that are labeled in accordance with the Tentative Final Monograph for OTC laxatives, or the leaf gel of *Aloe vera*, any product that contains as an ingredient any of the herbs listed below should include the following information on its label:

1. The specific herbs that are subject to this trade recommendation are:

| Botanical Name | Common Name | Plant Part |
|---|---|---|
| *Aloe* spp. | aloe | dried latex |
| *Cassia fistula* | Indian laburnum | fruit or pod |
| *Frangula alnus* | frangula | bark |
| *Frangula purshiana* | cascara sagrada | bark |
| *Rhamnus cathartica* | buckthorn | fruit |
| *Rheum officinale* | Chinese rhubarb | root |
| *Rheum palmatum* | Chinese rhubarb | root |
| *Senna* spp. | senna | leaf |
| *Senna* spp. | senna | fruit or pod |

*NOTE: Senna was formerly listed in the genus* Cassia, *including the following species:* Cassia angustifolia, C. obtusifolia, C. senna, *and* C. tora. *Bulk raw materials labeled as one of these species of* Cassia *should be* identified on finished consumer packages as "senna."

2. (a) Any dietary supplement that contains any of the ingredients listed in paragraph 1 above and that is labeled in accordance with 21 CFR 101.93 with an express or implied structure/function statement that states that the supplement is a laxative or provides releif for occasional constipation should be labeled in accordance with Federal regulations for laxative drug products for over-the-counter human use.

(b) The following statement should be included on the label of any other dietary supplement that contains any of the ingredients listed in paragraph 1 above in sufficient quantity to warrant such labeling:

*NOTICE: Do not use this product if you have abdominal pain or diarrhea. Consult a health care provider prior to use if you are pregnant or nursing a baby. Discontinue use in the event of diarrhea or watery stools. Do not exceed recommended dose. Not for long-term use.*

[NOTE: The State of California has established labeling requirements that supercede the AHPA recommendation for products sold in California. All dietary supplements that contain any amount of the above listed ingredients are required to bear the following label: *NOTICE: This product* contains (name of substance(s) and common name(s) if different). Read and follow directions carefully. Do not use if you have or develop diarrhea, loose stools, or abdominal pain because (insert common name) may worsen these conditions and be harmful to your health. Consult your physician if you have frequent diarrhea or if you are pregnant, nursing, taking medication, or have a medical *condition.* END NOTE.]

## VI. Pyrrolizidine Alkaloids (adopted July 1996)

AHPA recommends that all products with botanical ingredients which contain toxic pyrrolizidine alkaloids1 bear the following cautionary statement on the label:

*For external use only. Do not apply to broken or abraded skin. Do not use when nursing.*

1) Including but not limited to: *Alkanna tinctoria* (alkanet); *Anchusa officinalis* (bugloss); *Borago officinalis** (borage); *Crotalaria* spp., *Cynoglossum* spp., *Erechtites hieraciifolia, Eupatorium cannabinum* (hemp agrimony); *Eupatorium purpureum* (Joe Pye), *Heliotropium* spp., *Lithospermum officinale* (European gromwell); *Packera candidissima, Petasites* spp. (e.g., Butterbur); *Pulmonaria* spp. (e.g., lungwort); *Senecio jacobaea* (European ragwort); *Senecio vulgaris* (groundsel herb); *Symphytum* spp. (comfrey); and *Tussilago farfara* (coltsfoot).

* Borage seed oil is specifically exempt from the above label recommendation.

## VII. Known Adulterants (adopted July 1997)

AHPA recommends that appropriate steps be taken to assure that the following raw materials are free of the noted adulterant:

| Herb in Commerce | Adulterant |
|---|---|
| 1. Eleuthero root (*Eleutherococcus senticosus*) | 1. *Periploca sepium* root |
| 2. Plantain leaf (*Plantago lanceolata*) | 2. *Digitalis lanata* leaf |
| 3. Skullcap herb (*Scutellaria lateriflora*) | 3. Germander herb (*Teucrium chamaedrys*) |
| 4. Stephania root (*Stephania tetrandra*) | 4. *Aristolochia fangchi* root |

AHPA's Standards Committee is in the process of establishing appropriate testing methods to differentiate between each of the above listed herbs and its known adulterant. Also, the AHPA Botanical Raw Materials Committee has initiated the development of a *Botanical Adulteration Manual* that will provide information on all herbs in trade for which adulteration is known to be an issue.

## VIII. Kava (adopted September 1997; revised March 2002)

AHPA recommends the following dosage and labeling policies for products containing kava (*Piper methysticum*):

- Products containing kava should be formulated and labeled to limit consumption of total kavalactones to 300 mg per day;
- Labels of all products containing kava should bear the following or significantly similar statement:

*Caution: Ask a healthcare professional before use if you have or have had liver problems, frequently use alcoholic beverages, or are taking any medication. Stop use and see a doctor if you develop symptoms that may signal liver problems (e.g., unexplained fatigue, abdominal pain, loss of appetite, fever, vomiting, dark urine, pale stools, yellow eyes or skin). Not for use by persons under 18 years of age, or by pregnant or breastfeeding women. Not for use with alcoholic beverages. Excessive use, or use with products that cause drowsiness, may impair your ability to operate a vehicle or heavy equipment.*

## IX. Goldenseal (adopted March 1998)

AHPA recommends that its members refrain from labeling or marketing products that contain Goldenseal (*Hydrastis canadensis*) in any manner that suggests that the product masks drug testing.

## X. *Botanical Safety Handbook* (adopted July 1998; revised October 2001*)

AHPA recommends that any products that contain herbs classified in the *Botanical Safety Handbook* in Class 2b, 2c, or 3 be labeled according to the labeling classification for those classes.

- Class 2b is defined as not for use in pregnancy unless otherwise directed by a qualified expert.
- Class 2c herbs are those that are not to be used while nursing unless otherwise directed by a qualified expert.
- Class 3 is defined as herbs for which significant data exist to recommend the following labeling: *To be used only under the supervision of an expert qualified in the appropriate use of this substance.* Labeling must include proper use information: dosage, contraindications, potential adverse effects and drug interactions, and any other relevant information related to the safe use of the substance.

AHPA also recommends that products containing Class 3 herbs be labeled as not for general retail sale and that such products be marketed in a manner that prevents general retail sale.

Any product containing Class 3 herbal ingredients that is manufactured, formulated or controlled in a manner that removes the concern that is the cause of such classification shall be exempted from this recommendation so long as the manufacturer and marketer of the product have substantiation that this concern has been removed.

*This trade recommendation, as it affects Class 3, shall take effect on October 10, 2002, 12 months after its adoption by the board.

## XI. Disclosure of Added Constituents (adopted October 1999)

Whereas the Federal labeling regulations for dietary supplements require that labels list all ingredients in order of predominance, AHPA recommends, for any botanical raw material, whether sold as a botanical or as a concentrate; metabolite; constituent; or extract of a botanical, that:

- the ingredient declaration of bulk botanical raw material declare all ingredients by their common or usual name and in order of predominance, including but not limited to botanical extractives; excipients; fillers; binders; solvents that have not been removed; and added constituents;
- specification sheets for bulk botanical raw materials indicate for each such ingredient the percentage, or range of percentages, of the entire raw material represented by the ingredient, so that finished product manufacturers can determine the order of ingredients in a finished product containing the raw material;
- the common name of a botanical raw material to which a constituent has been added be in the form of: botanical; plant part; form; "with added" constituent, e.g.; "guarana seed extract with added caffeine"; "goldenseal leaf powder with added berberine";
- manufacturers and marketers of finished products containing any botanical raw material as described here label such products to include all ingredients as described here in order of predominance.

## XII. Pesticide Analysis for Ginseng (adopted November 1999)

AHPA recommends that processor and manufacturer members analyze cultivated ginseng (*Panax* spp.) for the presence of quintozene and related compounds by a validated methodology; provided that, any cultivated ginseng which is produced in a manner that assures that the ginseng is free of quintozene and related compounds is exempted from this recommendation; and further provided that, in lieu of such analysis by the processor or manufacturer, a guarantee or certification of analysis may be accepted from a supplier provided that the processor or manufacturer establishes the reliability of the supplier's analysis.

## XIII. Artistolochic Acid (adopted June 5, 2001)

AHPA recommends that no herbal dietary supplement product shall include any herbal ingredient that contains aristolochic acid; that bulk-packaged raw material containing aristolochic acid (e.g., all species of the genus *Aristolochia* which contain aristolochic acid; *Asarum canadense*; *Asarum europaeum*; *Asarum himalaicum*; etc.) shall be labeled for external use only. If scientific evidence establishes an acceptable safe tolerance level for aristolochic acid, the AHPA Board will reconsider this trade recommendation upon receipt of such evidence, and AHPA will support the development of such scientific evidence within its financial means.

AMERICAN HERBAL PRODUCTS ASSOCIATION

May 19, 2000

## Ephedra-containing Supplements Produced by Members Of Leading Trade Association Test Well in New Study

A recent analysis of ephedra-containing supplements revealed that American Herbal Products Association member companies manufacture products that perform well above the norm in quality testing.

The study was conducted by Dr. Bill Gurley of the College of Pharmacy at the University of Arkansas for Medical Sciences and is due to be published in the May, 2000 issue of the *American Journal of Health-System Pharmacy*. Dr. Gurley analyzed 20 different products, 9 of which are marketed by AHPA member companies. A total of 30 lots were tested including 12 from the 9 AHPA companies.

The study's author was critical of manufacturers, based on his report that the products contained anywhere from zero to 154% of the amount of ephedrine alkaloids stated on labels. A review of the result of AHPA member's products, however, tells an entirely different story.

Three of the 12 tested products manufactured by AHPA members did not state an alkaloid quantity on the label[1]. The other nine of these were found to contain between 84 and 109% of the claimed ephedrine alkaloids[2,3]. The mean ephedrine content of these samples was 98% of label claim. Federal labeling guidelines require that naturally occurring ingredients that are quantified on a label be present in an amount "at least equal to 80 percent of the value... declared on the label," and also permit reasonable excesses. All of the AHPA manufactured products were found to be well within this legal range.

[1] AHPA revised its trade recommendation for ephedra products in January, 2000 to require that alkaloids be quantified on product labels. There was no industry or regulatory requirement for such information prior to this. Gurley reports that all of his products were purchased in 1998 and 1999.

[2] Gurley informed AHPA staff that he believes his margin of error to be ±5%. While this may be overly optimistic, an adjustment for this error would further limit the tested range of these nine samples to 88 – 104% of label claim.

[3] One product contained 10.4 mg of total ephedra alkaloids of which 2.5 mg was specifically ephedrine. The label stated that it contained 10.0 mg ephedrine, and so was reported by Gurley to deliver only 25% of claim. There is, however, standard accepted terminology for results of analytical methods that do not separate the individual alkaloids but rather measure the total of all of the contained compounds. Such results are acceptably recorded as "Total alkaloids stated as ephedrine." For purposes of this review, it was

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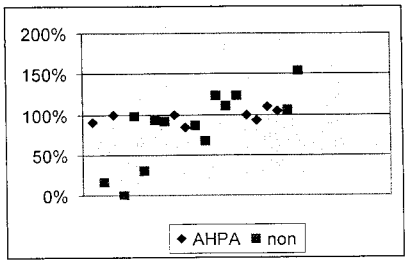
Here follows a graphic depiction of all products tested that made a label claim for quantity:




"Although Gurley's report is technically sound, we have identified some concerns with the conclusions that he has drawn," commented Dr. Joseph Betz, AHPA's Vice-President of Scientific & Technical Affairs. "Nevertheless, we are pleased to see that his analysis clearly shows that AHPA members, as responsible companies in the herb industry, are manufacturing their products in a manner that assures consumers that these products are accurately labeled."

A close reading of the entire study reveals that certain of the characterizations in Gurley's publication are, at best, confusing and in need of clarification.

- Gurley noted that five products contained (+)-norpseudoephedrine (NPSE), a naturally occurring ephedrine group alkaloid found in most of the Asian species of ephedra. His presentation of this information implied that some flaw in the regulation of supplements exempts ephedra products from the restrictions associated with drug scheduling. It is true that NPSE, in its purified form and under conditions specified in the regulations of the Drug Enforcement Administration (DEA), may be a Schedule IV controlled substance, subject to certain restrictions on use, sale and possession. However, DEA, while aware that ephedra may contain very small amounts of NPSE, has explicitly stated that ephedra products are not subject to scheduling, or even less restrictive "listing" requirements under the Controlled Substances Act. In summary, neither botanical ephedra nor crude extracts of ephedra have been the subject of any scheduling restrictions, and are therefore perfectly legal for use and sale.

assumed that this nomenclatural disagreement was not relevant, and that sample is here reported as 104% of label claim.

- One of the most sensational of Gurley's conclusions was his emphasis on what he described as "the dramatic variance in alkaloid content" between different lots of the same product. Ten products were tested for lot-to-lot variability. The article stated that six of these "showed virtually no difference in alkaloid content between lots." An examination of the other four cases, however, shows that the noted variations are based on comparisons in specific alkaloids, even though these were not identified on any of the products' labels. A review of the test data compared to the actual statements made on labels shows that only one product had a variation of more than 10% from one lot to the next.

The American Herbal Products Association was founded in 1983 by a group of companies active in the trade in botanicals. AHPA is now the national trade association and voice of the herbal products industry, comprised of domestic and foreign companies doing business as importers, growers, processors, manufacturers, marketers, and distributors of herbs and herbal products. AHPA serves its members by promoting the responsible commerce of products that contain herbs and that are used to enhance health and quality of life.

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For more information, contact Moira Saucer, AHPA, (301) 588-1171, ex. 107

Testimony of
Cynthia T. Culmo, R.Ph., Chairperson
Drugs, Devices, and Cosmetics Committee
Association of Food and Drug Officials
Before
Subcommittee on Oversight of
Government Management, Restructuring, and the District of Columbia
Committee on Governmental Affairs
United States Senate
Washington, D.C.
July 31, 2002

The Association of Food and Drug Officials Board of Directors, hereinafter referred to as AFDO, is pleased to offer written comments in addition to the oral comments presented by Cynthia Culmo, on July 31, 2002, to the Senate Governmental Affairs Subcommittee on Oversight of Government Management, Restructuring, and the District of Columbia hearing entitled, "When Diets Turn Deadly: Consumer Safety and Weight Loss Supplements."

AFDO is a 106 years old not for profit association that represents federal, state, and local regulatory members as well as industry associate members. AFDO develops and promotes uniform laws, regulations, and guidelines that result in more efficient and effective regulation along with enhanced cooperation and communication. AFDO has been a leader and active participant in many regulatory initiatives during the past many years at both state and federal levels. An activity of particular interest to this committee relates to our efforts to address the public health issues associated with products containing ephedrine; especially those labeled as dietary supplements which are advertised and promoted for weight loss, performance enhancement, and increased energy.

Our membership has many longstanding concerns related to the public health risks associated with dietary supplement products containing ephedrine alkaloids (hereinafter referred to as ephedrine) and other dietary supplements promoted for weight loss that contain stimulants. We last adopted a resolution in June 2001, urging the FDA to expedite a policy decision on this issue and to provide effective regulatory guidance on this difficult public health problem. We have submitted other resolutions concerning ephedrine containing dietary supplements in previous years. Considering the extensive documentation of serious adverse health effects associated with ephedrine-containing dietary

supplement products along with more recent developments, AFDO believes it is critical that FDA take strong and decisive actions regarding products that contain ephedrine. We submitted our June Resolution and request to Dr. Bernard Schwetz, then Acting Principal Deputy Commissioner, on September 18, 2001.

In an effort to stay focused on the issues at hand, we offer comments to the questions you posed regarding dietary supplements promoted for weight loss:

- **As a public health official, what has been your experience with weight loss supplements?**

The States and the FDA continue to receive serious adverse event reports (AERs). There are hundreds, if not thousands, of serious AERs for a plethora of products containing multiple pharmacologically active ingredients (multiple stimulants, diuretics, laxatives, metabolic blockers or stimulators, hormones, etc.). Many of the weight loss supplements contain herbs which have laxative effects such as senna, cascara, aloe, and rhubarb root. Labels of these supplements frequently do not warn consumers that ingredients in the product have laxative effects. Nor is there any mention of the dangers related to the daily consumption of such cathartic laxatives (e.g., severe electrolyte disturbances and heart arrhythmias). There are several supplements (some containing "chitin") that claim to "bind" fat so you can eat anything you want and "still not gain weight." This claim is not only unsound, but also provides potentially unsafe advice. Furthermore, the chitin in these products is commonly extracted from shellfish, but contains no warning of this fact on the product labels to alert those with shellfish allergies.

To support this concern with polyingredients in dietary supplement formulations, Bill J. Gurley, Ph.D., Associate Professor, Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences has reported that Ephedra-containing dietary supplements are rarely formulated as single ingredient products. Along with ephedrine alkaloids (ephedrine, pseudoephedrine, methylephedrine, norephedrine [phenylpropanolamine]) present in ma huang, most products also contain natural sources of caffeine (guarana, kola nut, green tea), additional stimulants (synephrine), and a host of other botanicals and amino acids (1). The pharmacokinetics (blood levels) of ephedrine following ingestion of supplements formulated as concentrated ephedra extracts is indistinguishable from that of synthetic ephedrine found in conventional dosage forms (2, 3). Thus, ephedrine and other sympathomimetic amines from botanical sources share the same risks for and consequences of interactions with conventional stimulants, hypoglycemic agents, antihypertensives, and monamine oxidase inhibitors that have been experienced with pharmaceutical products containing these ingredients. There are additional safety concerns for ephedra-containing supplements because of interactions among the individual phytochemical components. Thus these dietary supplement products pose risks above and beyond those seen with drugs containing ephedrine.

From a pharmacodynamic standpoint, ephedrine and caffeine each potentiate the other's cardiovascular and central nervous system stimulant effects, thereby increasing the risk of adverse events in susceptible individuals (1). Because of this enhanced health risk, the FDA has not allowed ephedrine/caffeine combinations in conventional OTC products since 1983 (1). Other phytochemical components in ephedra-containing dietary supplements appear to exacerbate ephedrine/caffeine pharmacodynamics. Catechins, a class of polyphenolic compounds found in high concentrations in guarana and green tea enhance the sympathetic activity of ephedrine and caffeine by inhibiting catechol-O-methyltransferase (4). Catechins are also readily absorbed into the systemic circulation and elicit their own inotropic effect on the heart (5, 6). Another common ingredient, *Citrus aurantium* (bitter orange) extract, provides an additional source of sympathomimetics (synephrine, octopamine), and has been shown to be arrhythmogenic in laboratory animals (1, 7). Recently, it was shown that multi-component ephedra-containing dietary supplements containing caffeine, catechins, and *Citrus aurantium* are more toxic in animal models than ephedra alone (8). St. John's Wort is yet another ingredient in some weight loss products, which when combined with ephedrine can increase the risk for serotonin syndrome. Taken together, these findings lend credence to adverse events reported in the medical literature and those submitted to the FDA's MedWatch program (9, 10).

As reported many times over the last eight years, dietary supplements containing ephedrine alkaloids from ephedra and other botanicals are commonly marketed for weight loss. People continue to experience serious adverse reactions from these products, including disabling or fatal heart attacks, strokes, seizures, and psychoses. The misleading and deceptive labeling and marketing for these products, which will be discussed later in the comments, may also be contributing to these adverse events.

Some weight loss dietary supplements make outrageous claims, e.g., "Exercise in a Bottle" marketed by former Dodger Steve Garvey claimed to be equivalent to exercising, or "Body Solutions" and the "Hollywood Diet" that each claim "Lose weight while you sleep." People at a minimum were and are defrauded by the advertising for these products. Eventually "Exercise in a Bottle" was removed from sale, but only after extensive resources were devoted to these efforts by the regulatory agencies.

Drug manufacturers have requested permission to make claims similar to those made for dietary supplements. Claims for over-the-counter (OTC) drugs cannot go outside a prescribed set of scientifically validated indications. Therefore, drug regulatory requirements prohibit such claims due to inadequate substantiation, yet dietary supplements routinely make these unsubstantiated claims and promotions. Consumers confuse dietary supplements promoted for weight loss with over-the-counter drugs which must be proven to be safe and effective while there are no comparable requirements for their dietary supplement counterparts. Nonetheless, dietary supplement products make safety and efficacy claims in their labeling and advertising.

Also, data on complaints from dietary supplements cannot be adequately evaluated since dietary supplement manufacturers are not required to record, investigate, or report complaints and/or injuries, unlike drug manufacturers. Because of civil proceedings involving personal injury, regulatory agencies are aware that dietary supplement companies are receiving thousands of reports of injuries related to their products, none of which have ever been reported to the FDA by the manufacturers. Yet they continue to report/advertise publicly that their products are safe and they haven't received reports of serious injuries. This was somewhat addressed two years ago, at the US Public Health Service meeting, on August 8, 2000, by Mr. Michael McGuffin, President, American Herbal Products (AHPA). He summarized an ephedra survey conducted by Arthur Andersen, LLP auditors on behalf of AHPA. He reported at this meeting the survey reflected a total of 25 serious AERs which were reported to the 14 respondents in 1999 and a total of 66 serious AERs were reported to the 14 respondents for the five-year period from 1995 to 1999. Upon questioning, he didn't know if they had been reported to the FDA, but FDA can confirm they've never received an AER from a dietary supplement manufacturer on these products. Interesting to note on this topic, Mr. McGuffin stated on ABC's Nightline, July 2000, "...but it would be just in—in—unbelievable if a manufacturer had any evidence that its product had—if, in fact, produced serious adverse effects, to think that they would not inform the agency. " Hard to believe, but true. Additionally, and perhaps not so surprising now, many problems with the validation and accuracy of that survey were discovered and disclosed.

Another issue concerning weight loss dietary supplements is that the industry routinely claims their products are not drugs, but they do advertise them as drugs under the guise of medical advice. Several firms have opted to print their product information in the Physician's Desk Reference for Nonprescription Drugs and Dietary Supplements (PDRNDDS) (previously the Physician's Desk Reference for Nonprescription Drugs). It should be noted that all material published in the PDR is provided to the publication and paid for by the manufacturers and is not reviewed or edited for content. The foreward to the 1999 PDRNDDS states:

> " The function of the publisher is the compilation, organization, and distribution of product information obtained from manufacturers. Each product description has been prepared by the manufacturer and edited and approved by the manufacturer's medical department, medical director, and/or medical consultant.
>
> In organizing and presenting the material in Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements the publisher does not warrant or guarantee any of the products described, or perform any independent analysis in connection with any of the product information contained herein. Physician's Desk Reference does not assume, and expressly disclaims any obligation to obtain and include any information other than that provided to it by the manufacture."

Therefore, the PDRNDDS is clearly a source of advertising and product information for dietary supplement manufacturers since there is no regulatory requirement for a patient package insert or labeling beyond that described in the Dietary Supplement Health and Education Act. The primary concern is that consumers will review this material and assume the 'science' of the content is equivalent to the information in the product descriptions submitted to PDR for prescription drug products; content that is guaranteed to have been previously reviewed by a source other than the manufacturer. A mislead consumer may well be the result.

DSHEA has resulted in a gross contradiction to its authors' prediction of a healthier nation pursuant to the total unregulated availability of dietary supplements. The reality seems to be quite contrary to the predictions. As the industry has grown enormously since DSHEA, and the types and numbers of "dietary supplement" labeled products have proliferated, there is no evidence that the health of Americans has improved due to increased access to supplements. As much as the dietary supplement industry has proclaimed the efficacy of their weight loss products, obesity remains a critical public health issue, and in fact, one that continues to increase in numbers. Not only has there not been any reportable improvement in the country's overall health, but quite the contrary, since the passage of DSHEA, reports of AERs have poured into the States and the U.S. Food and Drug Administration (FDA), even though it is estimated by Dr. Alexander Walker that less then one percent (1%) of the adverse events are reported to the FDA voluntary reporting system. Prior to DSHEA, most States report few if any AERs associated with dietary supplements to their agencies. In addition, the American Association of Poison Control Centers (AAPCC) did not record AERs for dietary supplements or herbs prior to DSHEA. (Attachment 1) If they did receive any, they were coded as drug AERs.

- **Did the passage of DSHEA in 1994 affect your ability to perform your job?**
  - **YES!**

DSHEA placed the burden of determining and proving health risks and disproving claims for weight loss products on regulatory agencies rather than on the firms marketing the products. This has made enforcement difficult and costly. For drugs, FDA can collect data on safety via the mandated pre-market safety studies and the post-marketing AERs. For dietary supplements, neither is required and both mechanisms are vehemently objected to by the dietary supplement industry.

DSHEA prevents regulatory agencies (and also discourages manufacturers) from evaluating risks versus benefits of dietary supplements. Risk/benefit evaluations are important components in this country's regulation of drugs, but are not required for these dietary supplement labeled products that also contain potent pharmacologically active ingredients, many of which are exactly the same synthetic ingredients found in drugs. DSHEA has added confusion because dietary supplements regulated as foods should not pose recognized health risks and should not be promoted to prevent or treat

diseases. Yet serious risks and safety concerns have arisen with the proliferation of products labeled as dietary supplements which contain pharmacologically active ingredients.

Many products use DSHEA to market conventional foods, e.g., beverages, cereals, and snack bars, that contain ingredients like ginkgo biloba, ephedrine, senna, and yohimbine commonly found in dietary supplements, but not specifically allowed in conventional foods where, prior to DSHEA, all ingredients had to be either approved food additives, generally recognized as safe, or prior sanctioned for safety.

DSHEA did not change the regulation of conventional foods, but has prompted manufacturers of some conventional foods, in their desire to obtain a portion of the dietary supplement market, to include these unapproved ingredients in their products and now label them as dietary supplements. Consumers, regulators, prosecutors, and juries are confused by the distinctions and overlaps between conventional foods and dietary supplements making states reluctant to take actions unless faced with flagrant violations that impact public health. Even then there are resultant political battles which adversely affect the abilities of the regulatory agencies to take these actions. The enforcement actions by the States are labor and time intensive, are done with great difficulty and fierce battles with industry and their political supporters. There are ongoing conflicts between good public health and industry's economic needs with politics frequently serving as the referee. The States and the federal government's failure or inability to take regulatory actions results in more conventional foods and dietary supplements in the marketplace containing ingredients that have not been thoroughly evaluated for safety. These conventional foods often display label claims allowed for dietary supplements under DSHEA, but not allowed for conventional foods. States also fail to take actions because of the confusion about the distinctions and overlaps between conventional foods and dietary supplements. Any attempt by FDA to clarify the confusion via regulations seems to be pre-empted or prevented by HHS, Congress, and/or the White House.

Dietary supplements are intended for human consumption. There is no provision in DSHEA for the use of the dietary supplements in animal feed, yet members of the American Association of Feed Control Officials report the appearance of vast numbers of these products on the market. The content of animal feed is tightly regulated. Any product designed for ingestion by animals is either a food or a food additive. Products marketed as dietary supplements must fit into one of those two categories, and frequently, they do not. Of special concern are those products targeted towards food producing animals that are intended for human consumption. A significant portion of time is now spent by feed control officials "chasing down" products that are in violation of feed regulations.

It is a federal responsibility to address DSHEA regulations. The States look to FDA and FTC, since they have (potential) resources that are unavailable to the States, to address these problems. But, politics and bureaucratic entanglements have prevented FDA and

FTC from accomplishing their responsibilities. It is easier for the states to ignore small problems, hoping FDA or FTC will act, than to expend resources in long, drawn-out investigations including possible industry lawsuits on a case-by-case basis. As AFDO has stated before, it's time to place the politics and money aside and act as the responsible public health agency that the general public considers FDA to be, and to which it is charged.

- **Have you seen evidence of harmful outcomes related to supplement use? What evidence?**
  - **Yes!**

AFDO would be more than remiss if Ephedrine wasn't discussed as the first example of harmful outcomes related to supplement use and the evidence associated with these harmful outcomes. As a quick reminder, ephedrine is extremely close in chemical structure to phenylpropanolamine and methamphetamine. (attachment 2) It is essentially a legal amphetamine-like substance and becomes even more so when combined with other stimulants.

- Many States have received AERs associated with weight loss supplements which contain ephedrine, and/or other stimulants. These include ingredients such as caffeine, theobromine, synephrine, forskolin, sida cordifolia, epitonin, citrus aurantium, yohimbe/yohimbine, and others. (attachment 3) Most of these the consumer, and others (medical professionals, public health officials, even some industry members), are completely unaware that they are potent stimulants. Some products (i.e. Xenadrine, NoPhedra, EAS Beta Blast, CytoTrim, etc.), or product regimes (Herbalife's Quick Start Gold Pack), may contain up to 161 ingredients or more! (attachment 2) Who knows what these multitudes of ingredients are doing within your body! They are quite simply a chemical soup waiting to have a time-bomb effect on unsuspecting persons. The ingredients interact with themselves, interact with other drugs, and there are drug-disease interactions.
    - California and other states have received reports and investigated serious injuries and deaths from dietary supplements. A woman in California used many different dietary supplements. She suffered from liver failure and subsequently died before receiving a liver transplant. Her death certificate listed the cause of death as polypharmacy from dietary supplements. This is not unlike other reports received by other states.
    - In California, two other deaths were investigated from bufotoxin, sold as an herbal product. One was due to misidentification of the bufotoxin and the other was due to accidental overdose. California also has investigated several cases of renal failure resulting from lack of Good Manufacturing Practices (GMP) leading to incorrect use of an herb that contained aristolochic acid, a renal toxin.

Other evidence of harmful outcomes has been related to contamination of these dietary supplements. FDA conducted a random sampling of products containing one of the 40 herbs commonly misidentified as artistolochic acid. 38 products were sampled and 18 of these products had aristolochic acid. There are more examples of heavy metal(s) contamination, filth contamination, and other adulterations.

Consumers are not only physically harmed and at risk with some of these products, but they are also harmed and deceived by the fraud associated with many of the products. When products containing ingredients like sea salt or dissolved oxygen are promoted to improve health and slow aging at a cost of hundreds of dollars a month for products with no nutritional or therapeutic value, and there is no science to back their claims, many suffer economic harm. Reports have been received where consumers stop using conventional vitamin and mineral supplements that provide real health benefits at minimal costs in favor of hyped supplements purported to contain some "wondrous" ingredient(s), or worse, discontinue prescription medications in favor of these miracle dietary supplements.

- **As a representative of the Association of Food and Drug Officials can you tell us what is happening at the state level with respect to weight loss supplement products (examples of states that are attempting to regulate, different approaches, obstacles to appropriate regulation, successes, shortcomings)?**

More than half the states have enacted or attempted to enact some form of legislation regarding ephedrine, some of which addressed dietary supplements with ephedrine. *(attachment 4)* Ohio and Nebraska had legislation regulating dietary supplements as prescription drugs, but were extensively lobbied by the dietary supplement industry and legislation was repealed or amended to include much lesser regulation. Texas, over a period of six years, attempted unsuccessfully to restrict dietary supplements containing ephedrine to a practitioner's prescription. Obstacles to this regulation included heavy lobbying by the industry and their representatives, intervention of state and federal legislators, and documentation of extensive spending on these efforts by industry and their lobbyists. Texas' fourth attempt to regulate dietary supplements with ephedrine did not propose to restrict the availability of ephedrine containing products, nor did they set dose restrictions. The rules outlined labeling requirements and warnings. Although the warning and labeling requirements represented some progress in protecting the public health, and in essence resulted in a national outcome for most of these products (the majority of these products are now labeled pursuant to Texas' requirements and are distributed nationwide), the States and the FDA continue to receive serious AERs. Additionally, industry continues to challenge efforts to appropriately label products with warnings, and opposes efforts to require mandatory reporting of adverse events.

In 1998, California, after great effort, adopted regulations requiring dietary supplements containing ingredients with stimulant laxative effects, of which the most common

products were those marketed as weight loss products, to display a label notice informing consumers not to use the product if they developed diarrhea, abdominal pain, or loose stools. Additionally there is legislation pending in California that would require dietary supplements containing ephedrine alkaloids, commonly marketed for weight loss, to list on the label the quantity of ephedrine alkaloids from herbal extracts, specific warnings, and FDA's MedWatch adverse event reporting line. This legislation would also prohibit sales to minors of dietary supplements containing ephedrine alkaloids. The Governor of California vetoed similar legislation two years ago stating that the regulation of dietary supplements was a matter of interstate commerce and the responsibility of the U.S. Congress. This veto also just happened to coincide with the documented significant contribution by Metabolife, Inc. to the Governor's campaign. The obstacles encountered by the States, FDA, and the FTC clearly demonstrate the issue of economics and politics versus public health.

The California Department of Health Services (DHS), along with many other states, works closely with their poison control centers in monitoring adverse reactions related to dietary supplements. Once an adverse reaction related to a dietary supplement has been identified, DHS, or the other state agencies, conducts a thorough investigation to identify the cause of the adverse reaction including obtaining the medical history of the patient, laboratory analysis, epidemiology study if necessary, and follow up with the distributor, importers and/or manufacturer. AFDO emphasizes that only regulatory agencies are equipped to conduct appropriate and complete dietary supplement adverse event investigations. Only regulatory agencies have lawful authority to oversee the manufacturing, distribution, professional practice, and public health areas. They can provide unbiased evaluations of the adverse events and share the results with the dietary supplement industry and the public.

California DHS reports also working closely with the dietary supplement industry to seek their cooperation on different issues. DHS initiated the Asian Medicine Operation Cooperation in the early 1990's to educate the users on the risk of Asian herbal products and to convince retailers and importers to remove unsafe products from sale, and manufacturers to reformulate and relabel their products to make them safe for use. This cooperative effort has achieved success in reducing exposure within the ethnic communities to unsafe herbal medicines, which have been associated with illness, death, and injury, and to do so with minimal impact upon cultural traditions.

- **Can you comment on how the US system of regulation for weight-loss supplements compare with other nations?**

The United States (US) has developed a rigorous and widely emulated system for evaluation and approval of new drugs. The United States, however, never emulated such countries as Japan and Germany, which accommodated national traditions by developing special regulations for traditional medicines (and dietary supplements in general). In Europe, the European Union (EU) is developing specific regulations on

botanical products under their DRUG system. The EU Directives regulate the manufacturing, distribution, marketing and approval of herbal products in addition to requirements for post market surveillance. Dietary supplements are generally prescription products in Europe and they aren't formulated, promoted, marketed, nor sold like they are in the US.

In China, one of the world's largest herbal producers, herbs used in Traditional Chinese Medicine are regulated as drug products. It has GMP regulations in place for manufacturers of herbal and dietary supplement products. China has also recently adopted good agricultural practices (GAP) for herbal products. In the U.S., dietary supplements are regulated as foods. There are currently no adopted GMPs and no proposal on GAPs.

In January 2002, Health Canada requested a recall of certain ephedrine containing products because a risk assessment concluded that these products posed a serious public health threat. Reports of adverse events included stroke, heart attacks, heart rate irregularities, seizures, psychoses and deaths. Currently in Canada, the maximum allowable dose for Ephedra/ephedrine in products is 8 mg ephedrine per single dose or 32mg ephedrine per day. Products containing Ephedra which were marketed for traditional medicine, were allowed to continue to be available, provided the products did not contain caffeine, and that the ephedrine content did not exceed 8 mg per dose up to a maximum of 32 mg per day. A previous press release issued by Health Canada in June 2001 advised Canadians not to use products containing the herb Ephedra, in combination with caffeine and other stimulants, for purposes of weight loss, body building or increased energy.

In 1999, Health Canada established the Office of Natural Health Products to ensure the safety of traditional herbal products, vitamins and mineral supplements, and homeopathic preparations. Currently, natural health products are regulated in Canada as either foods or drugs, however, new rules and modifications to Canada's Food and Drug Law will separate these products into their own regulatory category with a separate framework of enforcement. A proposed regulatory framework was set out in December 2001. The latest action of the Office of Natural Health Products was the April 2002 issuance of a draft guidance document entitled "Good Manufacturing Practices for Natural Health Products."

- **Are there any changes to the current law that you think would help ensure greater consumer protection?**

There are several changes to the current law that AFDO believes would ensure greater consumer protection:

- Prohibit multi-ingredient products, or limit to only one active ingredient per product. The polypharmacy within a bottle is a significant contribution to the harmful effects of these dietary supplements;

  - Require manufacturers and distributors to register with the FDA. Register products with FDA so that information about these products and their ingredients is readily available. If there is a formulation change, companies must submit a new registration before distribution;
  - Mandate AER reporting;
  - Create a single adverse event system within FDA so that product interactions can be readily identified and appropriately addressed. Make information from this system publicly available in a manner that health professionals, consumers and industry can readily access and use.
  - Create an EXPERT panel within FDA with the appropriate scientific expertise to review new dietary supplement ingredients applications. Provide authority for FDA to write regulations for new dietary supplement ingredient approvals;
  - Fund FDA! Fund FDA! Fund FDA! – user fees from this multi-billion dollar industry to support the program;
  - Create a specific Center **within FDA** for traditional medicines and Dietary Supplements for regulatory oversight – the public health focus for these products should be FDA, not NIH. Change NIH's authority and emphases so that research efforts focus on safety first, in addition to effectiveness research. When these changes are made, include funding for it;
- Support the utilization of AERs through all Congressional actions and publications. Congress funded FDA MedWatch & AERs – these are used repeatedly by FDA in actions to assure product safety. However, for dietary supplements it has been repeatedly stated that AERs cannot be used as the basis of actions to protect the public health. If the FDA can't use AERs, then the gold standard for safety should apply – i.e., adequate and well-controlled clinical trials affirming safety before the product can be marketed. The language for "significant or unreasonable risk" needs clarification and interpretation. AFDO also believes creating an EXPERT Medical Panel to review AERs would be beneficial, if the panel actually carries some authority for action.
- *Labels of all supplements except those containing only vitamins and minerals at 100 percent or less of the Reference Daily Intake should display FDA's MedWatch number and Internet address in a phrase similar to: "To report serious adverse events call 1-800-332-1088 or via the Internet at some short, convenient Internet address." Requiring that labels of dietary supplements display FDA's MedWatch number and Internet address, if they contain ingredients not essential in human nutrition, assures that consumers know who to call if they experience a serious adverse reaction. This requirement would improve FDA's awareness of adverse events experienced by individuals using these supplements.*

These changes would at a minimum improve the safety of these products for the general population and still allow the industry to sell their dietary supplements.

FDA has already effectively removed phenylpropanolamine, a compound with similar pharmacological effects and a partial metabolite of ephedrine, from the marketplace based on recommendations of its own Advisory Committee and a Yale University

School of Medicine study linking the drug to strokes. Yet since 1994, more strokes associated with ephedrine containing dietary supplements have been reported to FDA's MedWatch than for the almost 30 year period phenylpropanolamine was on the market. AFDO believes ephedrine should be considered equally dangerous for the same reasons and evidence.

On September 9, 2001, the National Football League (NFL) announced it has added ephedra, a genus of herbs from which the dietary supplement ephedrine is extracted, to its list of banned substances. The league based their decision on the available scientific evidence and the fact that three NFL players who died this year were found, on autopsy, to have ephedra in their systems. NFL league spokesman Greg Aiello, quoted in a Los Angeles Times article stated that "the purpose is to protect our players who operate in a very unique and stressful environment". Aiello also said "because of the research that's out there on ephedra, the commissioner [Paul Tagliabue] has reached the conclusion that it shouldn't be used by our players."

As evidenced by the previous paragraph, a non-healthcare professional, when presented with the evidence, concluded that ephedrine-containing dietary supplements promoted and marketed as "safe and natural" for uses such as weight loss, body building and increased energy, are dangerous.

It has also been alleged that there are healthcare professionals who tout the safety of these products are paid by industry to review the research, data, and FDA ephedra docket. AFDO believes that those healthcare professionals without such ties who have reviewed the research, data, and docket have concluded the products are dangerous, even when taken as directed. There are important issues of endorsements, professional conflict and appropriate disclosure, of which the public is generally unaware, that should be addressed.

Trustee J. Edward Hill, M.D., of The American Medical Association (AMA) stated, "Tobacco is the only product sold in America that kills when used as directed by the manufacturer." 2 Based upon the data and the statistics documented in the FDA docket on ephedrine adverse events reported, over 90% of the adverse events occurred when the products were taken as directed or at lesser doses. These statistics would seem to indicate that tobacco is no longer the only product that should be considered dangerous when used as directed by the manufacturer.

Another organization, the Public Citizen Health Research Group, very recently petitioned FDA via Secretary Thompson to ban the production and sale of dietary supplements containing ephedrine alkaloids. Their petition thoroughly and adequately addresses the data, statistics, research and science associated with our mutual concern regarding these products.

We would like to thank you for the opportunity to provide you with our comments, and for your time and consideration of this request. It is in the interest of public health safety

that AFDO urges Congress to assist the FDA, to act expeditiously, and to take actions in the true sense of good public health protection.

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American Association of Poison Control Centers
Page 1

Attachment 1

Homeopathic preparations

| YEAR | TOTAL | MODERATE | MAJOR | DEATH |
|---|---|---|---|---|
| 1993 | 1653 | 31 | 8 | 0 |
| 1994 | 2365 | 55 | 5 | 0 |
| 1995 | 2968 | 73 | 7 | 1 |
| 1996 | 3881 | 80 | 5 | 3 |

Dietary Supplement/herbals/homeopathic

| YEAR | TOTAL | MODERATE | MAJOR | DEATH |
|---|---|---|---|---|
| 1997 | 5502 | 117 | 12 | 0 |
| 1998 | 6914 | 165 | 19 | 0 |
| 1999 | 13,722 | 1641 | 744 | 10 |
| 2000 | 16,929 | 2483 | 641 | 15 |

Dietary Aids: phenylpropanolamine

| YEAR | TOTAL | MODERATE | MAJOR | DEATH |
|---|---|---|---|---|
| 1994 | 1868 | 232 | 16 | 1 |
| 1995 | 1703 | 258 | 6 | 0 |
| 1996 | 1534 | 216 | 9 | 1 |
| 1997 | 1472 | 186 | 6 | 1 |
| 1998 | 1403 | 182 | 12 | 0 |
| 1999 | 1125 | 141 | 11 | 1 |
| 2000 | 1052 | 148 | 5 | 0 |

Dietary Aids: phenylpropanolamine and caffeine

| YEAR | TOTAL | MODERATE | MAJOR | DEATH |
|---|---|---|---|---|
| 1994 | 265 | 42 | 1 | 0 |
| 1995 | 332 | 43 | 2 | 0 |
| 1996 | 315 | 43 | 2 | 0 |
| 1997 | 306 | 42 | 0 | 0 |
| 1998 | 263 | 32 | 4 | 0 |
| 1999 | 180 | 25 | 1 | 0 |
| 2000 | 142 | 28 | 4 | 0 |

Diet Aids: Other OTC

| YEAR | TOTAL | MODERATE | MAJOR | DEATH |
|---|---|---|---|---|
| 1994 | 209 | 10 | 0 | 0 |
| 1995 | 261 | 14 | 0 | 0 |
| 1996 | 289 | 27 | 0 | 0 |
| 1997 | 315 | 22 | 1 | 0 |
| 1998 | 339 | 27 | 0 | 0 |
| 1999 | 235 | 25 | 0 | 0 |
| 2000 | 350 | 54 | 2 | 0 |

Diet Aids: Other RX

| YEAR | TOTAL | MODERATE | MAJOR | DEATH |
|---|---|---|---|---|
| 1994 | 76 | 7 | 0 | 0 |
| 1995 | 280 | 31 | 4 | 1 |
| 1996 | 1945 | 152 | 11 | 1 |
| 1997 | 2741 | 280 | 21 | 1 |
| 1998 | 412 | 49 | 7 | 0 |
| 1999 | 178 | 28 | 1 | 0 |
| 2000 | 116 | 16 | 1 | 0 |

Diet Aids: Unknown

| YEAR | TOTAL | MODERATE | MAJOR | DEATH |
|---|---|---|---|---|
| 1994 | 202 | 28 | 0 | 0 |
| 1995 | 187 | 22 | 0 | 0 |
| 1996 | 185 | 20 | 2 | 0 |
| 1997 | 175 | 13 | 1 | 0 |
| 1998 | 193 | 17 | 2 | 0 |
| 1999 | 152 | 15 | 0 | 0 |
| 2000 | 194 | 34 | 2 | 0 |

Attachment 2

Weight Loss Plans

Weight loss plans promoted by dietary supplement marketers often involve the consumer taking a variety of products to achieve a desired effect. The effects of ingesting combinations of multiple nutritional products have not been fully examined for safety and effectiveness. Our concerns are: do these ingredients interact with each other or medications the consumer may be on; and what is the impact of poly-supplement use on other body systems and functions. Single products are often advertised as being most effective when used in combination with other products from the company line.

As an example, Herbalife's High Protein, Low-Carb program Quick Start Gold Pack requires the following products to be consumed together:

**Thermojetics High-Protein, Low Carb Weight Management Program Shake Mix**

| | | |
|---|---|---|
| Isolated soy protein | Aminogen | Citamin A |
| Fructose | Citrus pectin | Calcium pantothenate |
| Corn bran fiber | Psyllium husk | Papain |
| Powdered cellulose | Honey powder | Bromelain |
| Guar gum | Ginger root | Pyridocine |
| Potassium | Ascorbic Acid | Riboflavin |
| Calcium | Vitamin E | Thiamin |
| Dicalcium phosphate | Licorice root | Vitamin D3 |
| Rice fiber | Hawthorne berry | Folic Acid (25-30%) |
| Soy lecithin | Gotu kola | Biotin |
| Canola oil | Dandelion root | Chromium amino acid chelate |
| Carrageenan | Parsley | Chromium aspartate |
| Medium chain triglycerides | Papaya | Sodium molybdate |
| dl-methionine | Ferrous fumarate (Iron) | Chromium nicotinate |
| Fructooligosaccharides | Niacinaminde | Sodium selenite |
| Magnesium | Zinc oxide | Cyanocobalamin (Vitamin B12) |
| Licorice extract | Copper gluconate | |

**Thermojectics Gold**

| | | |
|---|---|---|
| Sida cordifolia (aerial) | Dried Green Tea extract | Quercitin |
| Advantra Z (bitter Orange Extract)(peel) | Dried Uva Ursi Extract | Bitter Orange |
| | Dried Cornsilk | Bioperine (dried Black Petter extract) |

**Soup Mix**

| | | |
|---|---|---|
| Milk protein concentrate | Salt | Hydrolyzed wheat protein (yeast extract) |
| Soy protein isolate | Onion powder | |
| Hydrolyzed gelatin | Hydrolyzed corn protein (thiamine, lactic acid) | |

**Drink Mix**

| | | |
|---|---|---|
| Hydrolyzed gelatin | Malic Acid | Aspartame |
| Whey protein isolate | Flavors | Colors |
| Citric Acid | Potassium citrate | |

**Protein Bar**

| | | |
|---|---|---|
| Corn syrup | Vitamin E | Biotin |
| High fructose corn syrup | Vitamin C | Iodine |
| Calcium caseinate | Niacin | Vitamin K |
| Whey protein | Iron | Vitamin B12 |
| Honey | Zinc | Canola oil |
| Peanut Butter (cottonseed oil, rapeseed oil, peanuts, salt) | Pantothenic Acid | Natural Peanut Flavor |
| | Vitamin B6 | Chicory Extract |
| Soy protein isolate | Vitamin A | Lecithin |
| Whey protein concentrate | Copper gluconate | Salt |
| Peanuts | Riboflavin | Bitter Orange |
| Glycerin | Thiamin | Codonopsis |
| Calcium | Vitamin D | |
| Magnesium | Folic Acid (20%) | |

**Thermojectics Formula 2-Multivitamin-Mineral and Herbal Tablets**

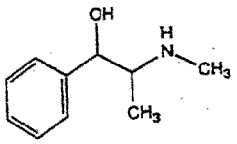
| | | |
|---|---|---|
| Vitamin A 1666iu | Iron | Broccoli |
| Vitamin C | Magnesium oxide | Carrot |
| Vitamin D | Zinc gluconate | Cauliflower |
| Vitamin E 10iu | Selenium | Citrus bioflavonoids |
| Thiamin | Copper gluconate | Cabbage |
| Riboflavin | Manganese gluconate | Garlic |
| Niacin | Chromium GTF, nicotinate & | Licorice root |
| Vitamin B6 | piocolinate 33mcg | Limonene |
| Folate (133mcg) | Potassium | Polyoids |
| Vitamin B12 | Vanadium | Spinach |
| Biotin | Bee pollen | Fungal enzymes |
| Pantothenic Acid | Choline bitartrate | |
| Calcium carbonate | Inositol | |

**Thermojectics Formula 3-Cell Activator**

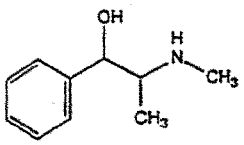
| | | |
|---|---|---|
| Magnesium | Aspartic Acid | Chlorella |
| Potassium | Glutamic Acid | L-glutamine |
| Citric Acid | Fumaric Acid | Cordyceps Fungus |
| Malic Acid | Inositol | Rhodiola |
| Succinic Acid | Cayenne Powder | Reishi Mushroom |

Attachment 3

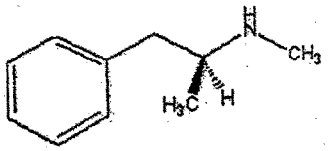
**EPHEDRINE**



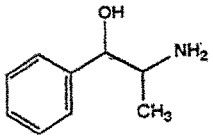

**PSEUDOEPHEDRINE**




**METHAMPHETAMINE**




**PHENYLPROPANOLAMINE (PPA)**



Attachment 4

Weight Loss Dietary Supplements

| **Stimulants** | **Laxatives** | **Diuretics** | **Other** | **Fiber** |
|---|---|---|---|---|
| Ephedra | Cascara sagrada | Caffeine | Chromium | Chitin |
| Yohimbine | Senna | Uva ursi | Hydroxy Citric Acid | Psyllium |
| Caffeine | Aloe vera | Burdock | Salicin (white willow) | Gluco-mannan |
| Theobromine | | | | |
| Synephrine | | | | |
| *Coleus forskolii* | | | | |
| | | | | |
| | | | | |

Synonyms of common stimulant dietary supplements

| **EPHEDRA** | **CAFFEINE** | **SYNEPHRINE** |
|---|---|---|
| Ma Huang | Guarana | Bitter orange |
| Sida cordifolia | Kola nut | *Citrus aurantium* |
| Morman tea | Green tea | Sour orange (leaf or flower) |
| Desert tea | Yerba mate | Green orange |
| Epitonin | Mate | Seville orange |
| | Bissey nut | Zhi shi |
| | | *Citrus reticulate* |
| | | *Fructus aurantii* |
| | | Mandarin |
| | | Tangerine peel |
| | | |
| | | |
| | | |
| | | |

Consumer Healthcare Products Association

**SUMMARY OF STATE RESTRICTIONS ON**
**EPHEDRINE, PSEUDOEPHEDRINE & PHENYLPROPANOLAMINE**

Revised 7/25/2001
Dates of enactment are included where statute or regulation has changed since 1990.

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| Alabama | None | None – EPH, PSE and PPA are regulated as precursor chemicals but OTCs exempted.<br>Ala. Code § 20-2-188(a). | None | None | None |
| Alaska | None | None | None | None | Unlawful to possess EPH, PSE or PPA with intent to manufacture methamphetamine.<br>Alaska Stat. § 11.71.020 (2000).<br>Unlawful to possess EPH, PSE or PPA with intent to manufacture an imitation controlled substance.<br>Alaska Stat. § 11.73.020. |
| Arizona | Schedule V for single ingredient EPH.<br>Ariz. Rev. Stat. § 36-2516.A.3 (1990). | EPH, PSE and PPA are regulated as precursor chemicals and distributors must register with state; safe-harbor OTCs are exempt at retail; DEA registrants submit fed'l forms in lieu of AZ reports.<br>Ariz. Rev. Stat. §§13-3404 and 3404.01 (1999). | Retail sales of EPH, PSE or PPA limited to 24 gm./transaction. Above threshold sales and suspicious transactions require reports.<br>Ariz. Rev. Stat. §13-3404 (1999).<br>Unlawful to sell EPH, PSE or PPA with knowledge precursor will be used for illicit substance.<br>Ariz. Rev. Stat. § 13-3404.01 (1999). | None | Unlawful to possess EPH, PSE or PPA with intent to manufacture illicit substance or to sell with knowledge precursor will be used for illicit substance.<br>Ariz. Rev. Stat. § 13-3404.01 (1999). |

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| Arkansas | Schedule V for single ingredient EPH (including combos with insignificant amounts of other active ingredients). Dept. of Health Rule-Ark. Controlled Substance List (effective Feb. 1996). However, all OTCs are exempt from CSA by statute.<br>Ark. Code Ann. § 5-64-608 (2001) | EPH, PSE and PPA are regulated as precursor chemicals. Retail distributors are exempt from keeping records of OTC transactions that conform to retail sales limits; manufacturers and wholesalers must submit suspicious order reports to the state board of pharmacy.<br>Ark. Code.Ann § 5-64-1005 (d), 1006 (2001)<br>Wholesale distributors must comply with Board of Pharmacy regulations regarding the storage and handling of List I Chemicals. Regulations mirror current federal law.<br>Ark. State Board of Pharmacy Code § 08-02-0006. | 3 pkg. limit per transaction on retail sales of EPH, PSE or PPA; 3 gm. / 96 pill single package limit; blister pack/unit dose packaging restriction; 18+ restriction w/proof of age ID requirement.<br>Exemptions for pediatric solids <=15mg. /dose, liquids <=15 mg./dose per 5 ml., and concentrated infant drops <=2 ml/dose and total package <=1 fl. oz.<br>Ark. Code. Ann § 5-64-1103 (2001)<br>Reckless disregard standard for unlawful distribution.<br>Ark. Code. Ann. § 5-64-1102 (2001) | None | Unlawful to possess > 5 grams of EPH and > 9 grams of PSE or PPA; exemption for retailers and health care providers, and manufacturers, wholesalers and distributors furnishing EPH, PSE and PPA to health care providers.<br>Unlawful possession shall constitute prima facie evidence of intent to manufacture methamphetamine.<br>Ark. Code. Ann. § 5-64-1101 (2001)<br>Unlawful to possess EPH, PSE, or PPA with intent to manufacture or distribute methamphetamine.<br>Ark. Code. Ann. § 5-64-1102 (2001) |
| California | None | EPH, PSE and PPA are regulated as precursor chemicals; includes registration and reporting by distributors.<br>Cal. Health & Safety Code §11106 (1997); §1100(e)(4); -(a)(16) (1996); and §11383 (1993).<br>Recordkeeping and reporting of threshold transactions of EPH, PSE & PPA. required.<br>Cal. Health & Safety Code §11106 (1997). | 3 pkg./9 gm. limit per transaction on retail sales of EPH, PSE or PPA; exempts pediatric liquids, incl. concentrated infant drops. Preempts all CA local ordinances restricting retail sales EPH, PSE and PPA products.<br>Cal. Health & Safety Code §§11100, 11106 (1999). | None | Unlawful to possess EPH or PSE with intent to manufacture methamphetamine<br>Cal. Health & Safety Code § 11383 (1997). |
| Colorado | Schedule II for EPH with exemption for products exempt from federal CSA (i.e., OTC products).<br>Col. Rev. Stat. § 18-18-418(2). | None | None | None | None |
| Connecticut | None | None | None | None | None |

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| Delaware | None | None | None | None | None |
| District of Columbia | None | None | None | None | None |
| Florida | Prescription drug status for EPH with exemptions for specific OTC product formulations in compliance with FDA.<br>Fl. Stat. Ann. § 499.033 (1995). | None | None | Prohibits advertising or labeling of ephedrine products for unapproved uses.<br>Fl. Stat. Ann. § 499.033. | Prohibits possession of any precursor chemical with intent to manufacture a controlled substance.<br>Fl. Stat. Ann § 893.033 and.149. |
| Georgia | PSE listed as a Dangerous Drug but OTC formulations are exempt.<br>Ga. Code § 16-13-71(b)(806) and (c)(23). | None | None | None | None |
| Hawaii | Local ordinance in Honolulu prohibits sales of ephedrine-containing dietary supplements but exempts FDA-approved OTC drugs from prohibition; prohibits sale of *any* EPH product to anyone under 18 years.<br>City Ord. for City of Honolulu (1996). | EPH, PSE and PPA are regulated as precursor chemicals but OTCs exempted.<br>Haw. Rev. Stat. § 329-64(a)(4).<br>Non-retail distributors must file copies of federal registration with state.<br>Haw. Rev. Stat. § 329-64(b) (1999). | DEA registrants must file copies of suspicious order reports with state.<br>Haw. Rev. Stat § 329-64(b) (1999).<br>Unlawful to sell EPH, PSE or PPA with knowledge that chemicals will be used to manufacture controlled substance.<br>Haw. Rev. Stat. § 329-65 (1999). | Prohibits sale of any EPH product labeled for ecstasy, euphoria, sexual sensation or legal "high".<br>Haw. Rev. Stat. § 329-64(e)(1999). | Unlawful to possess EPH, PSE or PPA with intent to manufacture or to sell with knowledge that chemicals will be used to manufacture controlled substance.<br>Haw. Rev. Stat. § 329-65 (1999). |
| Idaho | Schedule II for EPH, PSE & PPA; exemption for OTC products unless possessed with intent to manufacture meth.<br>Idaho Code § 37-2707 (1998).<br>Prescription drug status for EPH with list of exempted products by brand name.<br>Bd. of Pharmacy Rule No. 158 (revised 1994). | None | None | None | Possession with intent to manufacture methamphetamine nullifies exemption and converts substance to Schedule II.<br>Idaho Code § 37-2707 (1998). |

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| Illinois | Schedule V for EPH with exemptions for specific OTC product formulations.<br>720 Ill. Rev. Stat. Ch. 570, §§ 210(g) and 216(a) (1998). | None | None | Prohibits advertising and labeling of EPH for unapproved uses.<br>720 Ill. Rev. Stat. Ch. 570, § 216(b) (1998). | Prohibits possession of any methamphetamine manufacturing chemical (includes EPH, PSE or PPA) with intent to manufacture methamphetamine.<br>720 Ill. Rev. Stat. Ch. 570/401(ii) (1999). |
| Indiana | None | None | None | None | Prohibits possession of 2 or more chemical reagents (includes EPH, PSE or PPA) with intent to manufacture methamphetamine.<br>Ind. Code §35-48-4-14.5(b) (1999). |
| Iowa | Schedule V for EPH with exemptions for specific OTC product formulations.<br>Iowa Code § 124.212 (1997). | None – EPH, PSE and PPA are regulated as precursor chemicals but OTCs exempted.<br>Iowa Code § 124B.6.4. | Prohibits sale of EPH or PSE if person knows or should know product will be used as precursor to an illegal substance.<br>Iowa Code § 124.401.3 (1997). | None | Prohibits possession of EPH or PSE with intent to manufacture an illicit substance or for other than a medicinal use.<br>Iowa Code § 124.401.4 (1997). |
| Kansas | Schedule V for single ingredient EPH.<br>Kan. Stat. Ann. § 65-4113. | None – EPH, PSE and PPA are regulated as precursor chemicals but OTCs exempted. Kan. Stat. Ann. §65-7003 and § 65-7007(c)(3) and (4) (1999).<br>Kansas Bureau of Investigation required to develop and maintain program to inform retailers about meth problem and devise procedures and forms for suspicious purchases, thefts or other transactions involving any nonprescription, over-the-counter medicines. Reporting by retailers is voluntary and retailers reporting information in good faith are immune from civil liability. Kan. Stat. Ann. §65-7008 (1999). | Unlawful to sell EPH, PSE or PPA with knowledge or if seller should reasonably know chemical will be used to manufacture any illegal substance.<br>Kan. Stat. Ann §65-7006(b) (1999). | Prohibits marketing of EPH drug products for stimulation, mental alertness, weight loss or increased energy.<br>Kan. Stat. Ann. §65-7006(c) (1999). | Unlawful to possess EPH, PSE or PPA with intent to manufacture or to sell with knowledge that chemical will be used to manufacture any illegal substance.<br>Kan. Stat. Ann. §65-7006(a) (1999). |
| Kentucky | None | None | None | None | None |

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| Louisiana | Prescription status for EPH with exemptions for specific product formulations in compliance with FDA. Dep't. may exempt other products for valid medicinal use.<br>La. Rev. Stat. Ann. § 40:962.1 (1995); La. Admin. Code §48:1.3945 (1995). | None – EPH, PSE and PPA are regulated as precursor chemicals but OTCs exempted.<br>La. Rev. Stat. Ann. § 40:976.1.H. | None | Prohibits advertising and labeling of EPH for unapproved uses.<br>La. Rev. Stat. Ann. § 40:962.1 (1995); La. Admin. Code § 48:1.3945 (1995). | None |
| Maine | None | None | None | None | None |
| Maryland | None | None | None | None | None |
| Massachusetts | None | None | None | None | None |
| Michigan | Prescription required to possess more than 10 grams EPH, single ingredient or in combination.<br>Mich. Comp. Laws. Ann. §14.15 (17766c) (1996).<br>Schedule V for EPH with exemptions for specific formulations of drugs and dietary supplements.<br>Mich. Comp. Laws. Ann. §14.15 (7220(1)(c)) (1999). | Prohibits sale of dietary supplements or food containing EPH to anyone under 18 years old.<br>Mich. Comp. Laws. Ann. §14.15 (7339(1)) (1999). | None | Prohibits ads for EPH dietary supplement products as providing euphoria, ecstasy, altered mental state, heightened sexual performance or increased muscle mass.<br>Mich. Comp. Laws. Ann. §14.15 (7339(2)) (1999). | Unlawful to possess more than 10 grams of EPH, without a prescription; exemptions for certain OTC combo products.<br>Mich. Comp. Laws. Ann. §14.15 (17766c) (1995). |
| Minnesota | Prescription status for EPH with exemptions for specific OTC product formulations in compliance with FDA.<br>Minn. Stat. §151.135 (1998) | None – EPH, PSE and PPA are regulated as precursor chemicals but OTCs exempted.<br>Minn. Stat. § 152.0974(4). | Prohibits sale of EPH, PSE or PPA if person knows or reasonably should know product will be used to manufacture an illegal substance.<br>Minn. Stat. §152.135 (1998). | Prohibits advertising, marketing & labeling of EPH for unapproved uses.<br>Minn. Stat. §152.135 (1998) | Prohibits possession of EPH, PSE or PPA with intent to manufacture an illegal substance.<br>Minn. Stat. §152.135 (1998). |
| Mississippi | None | None | None | None | None |

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| Missouri | Schedule IV for single ingredient EPH including combos with therapeutically insignificant quantities of other active ingredients.<br>Mo. Rev. Stat. § 195.017.8(6) (1995). | EPH, PSE and PPA are regulated as precursor chemicals.<br>Mo. Rev. Stat. §195.010 (2001)<br>Suspicious transaction reports filed with with U.S. AG must be copied to the chief law enforcement official with jurisdiction.<br>Mo. Rev. Stat. § 195.515 (2001)<br>Lawful sale, transfer, furnishing or receipt of OTCs is exempt from proper ID and state department of health reporting requirements regarding precursor chemicals.<br>Mo. Rev. Stat. § 195.400 (2001) | 3 pkg. limit per transaction on retail sales of EPH, PSE or PPA; exemption for pediatric OTCs; sales limited to packages with <=3 gm. base EPH, PSE, PPA with safe harbor or unit dose packets.<br>Mo. Rev. Stat. §195.417, 418 (2001) | Prohibits marketing of ephedrine or pseudoephedrine for unapproved uses.<br>Mo. Rev. Stat § 195.248 (1996). | Possession of > 24 gm. of EPH, PSE or PPA shall be prima facie evidence of intent to deliver and manufacture methamphetamine; exemption for practitioners, or for any product possessed in the course of legitimate business.<br>Mo. Rev. Stat § 195.235, 246 (2001) |
| Montana | Schedule V for single ingredient EPH (including combos with therapeutically insignificant amount of other active ingredients).<br>Mont. Code Ann. § 50-32-229(5) (1997). | None | None | None | Unlawful to possess EPH, PSE or PPA with intent to manufacture a dangerous drug<br>Mont. Code Ann. § 45-9-107 (1999). |

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| Nebraska | Schedule IV for EPH with exemptions for named FDA-approved OTC products.<br>Neb. Rev. Stat. § 28-405(IV)(g)(2) (1996). | None | Unlawful to sell EPH, PSE, or PPA if seller knows that transferee will use product to manufacture a controlled substance; unlawful to sell with reckless disregard as to how the product will be used.<br>Neb. Rev. Stat. § 28-401 *et seq.* (2001)<br>Rx status for EPH, PSE and PPA products unless they are packaged in "safe harbor" packaging (blister packed, no more than 3 grams base, 2 tablets per blister OR liquid with no more than 3 grams base).<br>Neb. Rev. Stat. § 28-401 *et seq.* (2001) | None | No person shall possess EPH, PSE or PPA with the intent to manufacture methamphetamine.<br>Neb. Rev. Stat. § 28-401 *et seq.* (2001) |
| Nevada | Schedule III for EPH; exemptions granted by brand name.<br>Nev. Admin. Code §453.530(6)-(8) (revised 1994). | None | None | None | None |
| New Hampshire | None | None | None | None | None |
| New Jersey | None, but nonprescription distribution of EPH limited to 50 mg. dose.* | None | None | None | None |
| New Mexico | Prescription required for EPH with exemption for OTCs in compliance with FDA and containing 00.5% or less of ephedrine.<br>Bd. of Pharmacy Reg. No. 17 (1994). | None, EPH and PSE are regulated as precursor chemicals but OTCs exempted.<br>N.M. Stat. Ann. § 30-31B-2.L. | Albuquerque local ordinance limits sales to 3 packages or 100 pills in a single transaction.<br>Albuquerque City Ordinance (1999) | None | None |
| New York | None | None | None | None | None |

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| North Carolina | None | None | None | None | Prohibits possession of any precursor chemical (including EPH, PSE or PPA) with intent to manufacture methamphetamine.<br>N.C. Gen. Stat. § 90-95(d). |
| North Dakota | None, but nonprescription distribution of EPH limited to 25 mg. dose.* | None | None | None | None |
| Ohio | Schedule V for EPH; exemptions granted by brand name by Bd. of Pharmacy, see regulations.<br>Ohio Rev. Code § 3719.44 and OAR § 4729-12-01 thru -10 (1994 & revised 1996). | None | None | Prohibits marketing dietary supplement containing EPH for euphoria, ecstasy, buzz or high or heightened sexual performance.<br>Ohio Rev. Code §3719.44 (1998). | Assembly or possession of precursor chemicals with intent to manufacture methamphetamine is a third-degree felony. Ohio Rev. Code § 2925.041 (2001) |
| Oklahoma | Schedule IV for EPH with list of exempted brand name products and criteria for further exemptions.<br>Okla. Stat. Title 63, § 2-210.A.34 (revised 1996) | None, EPH, PSE and PPA are regulated as precursor chemicals but OTCs exempted.<br>Okla. Stat., Title 63, §2-327. | None | Dietary supplements containing naturally occurring ephedrine alkaloids that are exempt from controlled substances list cannot make certain advertising/marketing claims regarding euphoria, sexual performance or muscle mass development.<br>Okla. Admin. Rule 475:10-1-24 | Unlawful to possess EPH or PSE with the intent to manufacture a controlled dangerous substance.<br>Okla Stat., Title 63, § 2-401(F).<br>1999 amendment clarifies that OTC exemption from precursor controls in controlled substance law does not apply if person knows product will be used to manufacture methamphetamine.<br>Okla. Stat., Title 3, § 2-327 (1999). |

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| Oregon | Schedule II for EPH; exemptions granted by brand name and blanket exemption for products approved for OTC sales by FDA.<br>Ore. Admin. Rule 885-80-022 and -028 (revised 1995). | EPH, PSE and PPA regulated as precursor chemicals; EPH combination OTCs exempted. Distributors licensed by board of pharmacy and retailers in compliance with 3 pkg./ 9-gm. sales limit exempt from reporting requirements.<br>Or. Rev. Stat. § 475.940, 950 (2001)<br>Reporting requirement to state police upon discovery of theft or loss of precursor substance.<br>Or. Rev. Stat. §475.955 (2001) | 3 pkg./9 gm. limit per transaction on retail sales of EPH, PSE or PPA; exemptions for pediatric solid dose <=15mg. /dose, liquids <=15 mg. /5 ml. liquid product and concentrated infant drops <=2 ml/dose and pkg. content <=1 fl. oz.; exemption for dietary supplements containing naturally occurring ephedrine alkaloids (ephedra content must be <=15 percent of total weight of dietary supplement).<br>Or. Rev. Stat. §475.(__) Chapter 615, Laws of 2001) | | Unlawful to possess > 9 gm. of EPH, PSE or PPA; exemption for physicians, pharmacists, retail distributors, wholesalers, manufacturers, warehousmen or common carriers; household exemption for persons in possession of <24 gm. of EPH, PSE or PPA under circumstances consistent with typical medicinal or household use (under circumstances consistent with typical medicinal or household use as indicated by storage location, and possession of products in a variety of strengths, brands, types, purposes and expiration dates).<br>Or. Rev. Stat. §475.(___ ) Chapter 615, Laws of 2001 |
| Pennsylvania | Unlawful to sell EPH to any person under 18 years old; exemptions for specific OTC formulations in compliance with FDA and distributed for legitimate medicinal use in a manner to reduce likelihood of abuse.<br>18 Pa. Cons. Stat. § 6316 (1997). | None, EPH, PSE and PPA are regulated as precursor chemicals but OTCs exempted.<br>35 Pa. Cons. Stat. § 885(b)(4). | None | None | None |
| Rhode Island | None | None | None | None | None |
| South Carolina | None | None | None | None | None |
| South Dakota | Schedule III for EPH; Dept. of Health exempts specific product formulations by regulation.<br>S.D. Laws § 34-20B-19 (1995, amended in 1997 by H.B. 1028). S.D. Admin. R. § 44:58:13:01 (1997). | None | None | None | None |

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| Tennessee | Prescription status for EPH with exemptions for specific OTC product formulations in compliance with FDA.<br>Tenn. Code § 39-17-431 (1995). | None | None | Prohibits advertising & labeling ephedrine for unapproved uses.<br>Tenn. Code § 39-17-431 (1995). | None |
| Texas | None | None, EPH, PSE and PPA are regulated as precursor chemicals but OTCs exempted.<br>Tex. H&S Code § 481.077(I).<br>Unlawful to provide a dietary supplement containing ephedrine to any one under 18 years old.<br>Tex. H&S Code §431.022 (1999). | None | None | None. |
| Utah | None | None, EPH, PSE and PPA are regulated as precursor chemicals but OTCs exempted.<br>Utah Code Ann. § 58-37c-8. | None | None | Prohibits possession of >12 gm. of EPH or PSE; exemption for legitimate sales.<br>Utah Code Ann. § 58-37c-20 (1998) |
| Vermont | None | None | None | None | None |
| Virginia | Prescription required to sell EPH to any minor in combination with caffeine.<br>Va. Code Ann. § 18.2-248.5. | None | None | None | None |

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| Washington | Prescription status for any products containing EPH; exemptions granted by brand name.<br>Wash. Admin. Code §246-883-030. | EPH, PSE and PPA regulated as precursor chemicals.<br>Reports must be submitted to the state board of pharmacy by manufacturers, wholesalers and retailers on EPH, PSE and PPA sales and transfers and the receipt of EPH, PSE and PPA from out-of-state sources.<br>Proper identification requirement for purchase of precursor substance.<br>Wash.Rev.Code § 69.43.010, .020 (2001)<br>Wash. Admin.Code § 246-s-107 , § 147-s-2 (2001)<br>Manufacturers and wholesalers must report suspicious transactions in writing to board of pharmacy.<br>Rev. Wash. Code § 69.43. (__) Chapter 96, Laws of 2001<br>Manufactures and wholesalers are required to maintain records of sales and transfers of EPH, PSE and PPA.<br>Rev. Wash. Code § 69.43. (__) Chapter 96, Laws of 2001 | 3 pkg./9 gm. limit per transaction on retail sales of EPH, PSE or PPA.<br>Rev. Wash. Code § 69.43. (__) Chapter 96, Laws of 2001<br>Exemptions for pediatric solid dose & liquids<=15mg./dose, and concentrated infant drops <=2 ml/dose.<br>Rev. Wash. Code § 69.43. (__) Chapter 96, Laws of 2001<br>Preempts all WA local ordinances restricting retail sales of EPH, PSE and PPA products.<br>Rev. Wash. Code §69.43. (__) Chapter 96, Laws of 2001 | None | Unlawful to possess >15 gm. EPH, PSE and PPA; exemptions from possession limit for pharmacy, practitioner, distributor, retailer and "typical medicinal/household" use (under circumstances consistent with typical medicinal or household use as indicated by storage location, and possession of products in a variety of strengths, brands, types, purposes and expiration dates).<br>Unlawful to purchase more than 9 grams in a 24 hour period.<br>Wash. Rev. Code § 69.43.__ (Chapter 96, Laws of 2001) |
| West Virginia | None | None | None | None | None |
| Wisconsin | Schedule IV for EPH including combos with therapeutically insignificant quantities of other active ingredients.<br>Wisc. Stat. § 161.20(3)m. Wisc. Stat. § 961.01(12g) (1996). | None | None | None | None |

| State | Restricted Availability of EPH, PSE or PPA | Requirements for Distributors of Over-the Counter EPH, PSE or PPA | Restrictions and/or Limits on Retail Sales of OTCs w/ EPH, PSE or PPA | Restrictions on Marketing, Advertising and Labeling | Limitations on Possession of EPH, PSE and PPA |
|---|---|---|---|---|---|
| Wyoming | Prescription status for single ingredient EPH and certain combination EPH (25 mg. ephedrine in combination with less than 400 mg. Guaifenesin per dose).<br>Wyoming Board of Pharmacy Rules, Chapter XI, Section C (1999). | None | None | None | Unlawful for any person to knowingly or intentionally possess EPH, PSE or PPA with the intent to engage in a clandestine laboratory operation, W.S. 35-7-1058(a)(i), or to sell, distribute or otherwise supply EPH, PSE or PPA knowing it will be used for a clandestine laboratory operation.<br>Wyo. Stat. 35-7-1058(a)(iii). |

* A 1994 National Association of Boards of Pharmacy (NABP) newsletter summarizing restrictions on ephedrine reported the indicated restrictions in New Jersey and North Dakota. However, a search of the relevant statutes and administrative codes and subsequent phone calls to the boards of pharmacy in those states could not verify those restrictions or locate a statutory or regulatory citation for those restriction. CHPA could not confirm whether these restrictions do exist or were reported in error.

CHPA/mds Revised 7/25/01


*Producers of Quality Nonprescription Medicines and Dietary Supplements for Self-Care*

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION®

**Statement Submitted for the Record**
**On**
**The Regulation and Safety of Dietary Supplements**

**Senate Governmental Affairs Committee**
**Subcommittee on Oversight Management, Restructuring and the District of Columbia**

**The Honorable Richard Durbin, Chairman**

**July 31, 2002**

Thank you for allowing the Consumer Healthcare Products Association ("CHPA") to provide written comments for the record concerning the government regulation of dietary supplements in the areas of product safety, effectiveness, and labeling.

Established in 1881, CHPA represents over 200 companies who are involved in the manufacturing, distribution, marketing and development of nonprescription, over-the-counter (OTC) medicines and dietary supplements. Dietary supplement products manufactured by CHPA member companies include vitamins and minerals, such as vitamins C and E, folic acid, calcium and iron, and a variety of other substances commonly used to supplement the diet.

CHPA would like to direct its comments toward two important issues that have been raised by the Committee for the purposes of this hearing: first, what government and industry standards are in place to ensure the quality, effectiveness, and safety of dietary supplements; and, second, the proper action Congress can take to ensure the ongoing safety, quality, appropriate use, and proper labeling of dietary supplements.

**Government and Industry Standards**

Dietary supplements provide consumers with valuable self-care health options that are safe, effective, accessible, convenient and economical. Dietary supplements include a wide variety of products that are commonly used by consumers to promote and maintain healthy body functions. A large and rapidly expanding body of research suggests that

increasing the intake of specific nutrients and supplements to a healthy diet may be helpful in protecting against debilitating and deadly diseases, such as osteoporosis, heart disease, enlarged prostate and certain birth defects. According to industry sources, approximately three in five consumers—59 percent—currently take supplements on a regular basis to maintain and improve their health. Dietary supplements are sold through a variety of retail sources including pharmacies, grocery stores, mass merchandisers, catalog and Internet sales, and direct personal sales.

The U.S. Food and Drug Administration (FDA) and the Federal Trade Commission (FTC) have regulatory authority over the safety and marketing of dietary supplements. Specifically, supplements are regulated under the Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Dietary Supplement Health and Education Act (DSHEA). Where DSHEA does not address a particular aspect of regulation, dietary supplements are generally subject to regulation as a subset of "foods" under other provisions of the FD&C Act. Under the Federal Trade Commission Act, FTC has full authority to ensure that dietary supplement claims are truthful, not misleading, and substantiated—the same authority FTC exercises over claims for other every other product under its jurisdiction, including OTC drugs.

*FDA Regulation of Dietary Supplements*

FDA oversees the regulation of the manufacturing, packaging and labeling of dietary supplements. The passage of DSHEA in 1994 provided the agency with additional authority to take action against any dietary supplement product that is found to be unsafe or that makes unsubstantiated claims or unapproved drug claims. FDA also has legal authority to move against any dietary supplement that presents a significant or unreasonable risk of injury or illness, as demonstrated by the agency's action to remove gamma butyrolactone (GBL, a.k.a. "blue nitro") from the market in 2000.

Current Good Manufacturing Practice (GMP) regulations govern the manufacturing of dietary supplements as "foods." CHPA has strongly urged FDA to propose new rules that would require companies manufacturing dietary supplements to meet Good Manufacturing Practices (GMPs) specifically geared to dietary supplements. A new dietary supplement GMP proposal that is nearing publication is expected to raise the bar even higher for these products, further assuring consistent product quality. CHPA has made GMPs an industry priority and has continued to meet with FDA and the Office of Management and Budget to expedite the publication of a proposed rule, which FDA has strongly indicated will be issued by the end of the year.

*FTC Regulation of Dietary Supplement Advertising*

The Federal Trade Commission (FTC) regulates advertising of dietary supplements. The agency issued comprehensive advertising guidelines for dietary supplements in November 1998 that reaffirms longstanding law that advertising for dietary supplements (like all other consumer products) must be truthful, not misleading and substantiated. The FTC provides guidance for evaluating the adequacy of substantiation, limitations on consumer

testimonials, expert endorsements, and claims based on historical or traditional uses of dietary supplements. These guidelines apply to all forms of advertising, including broadcast, Internet and print ads.

The FTC can, and does, take action against products that make untruthful, misleading, or unsubstantiated claims. FTC has conducted several "Internet sweeps" in the past several years that have targeted dishonest or unsubstantiated advertising on the Worldwide Web. For example, in June of 2001, the FTC's "Operation Cure.All", a coordinated effort with the FDA, Health Canada and various state attorneys general, resulted in FTC enforcement actions against six dietary supplement companies for making false and unsubstantiated health and safety claims. Five of the companies have agreed to settle the charges, and the Commission has filed a complaint against the sixth company in federal district court. The FTC maintains an active enforcement presence in the industry, giving priority to those situations presenting serious safety concerns.

**Congress Should Oppose Changes that Would Undermine DSHEA**

Congress should oppose efforts to add new layers of regulation that would undercut the intent of DHSEA. FDA officials have testified before Congress that they believe dietary supplements are now appropriately regulated, allowing consumers to make many of their own health care decisions. Nevertheless, American consumers have a right to expect that their dietary supplements will continue to be safe, effective and of high quality. To ensure that these goals are met, Congress, FDA and the industry must do the following:

**Safety**

- **The existing adverse event reporting (AER) system for dietary supplements at FDA must be improved.** Health professionals and consumers may file adverse event reports, or AERs, voluntarily with FDA when a serious reaction or product problem occurs. FDA must be given the resources to strengthen its data collection, scientific evaluation and management efforts associated with adverse events for dietary supplements. For small businesses, industry is in the process of developing and implementing a third party reporting system to complement the current FDA system.

**Quality**

- To ensure quality, **FDA must immediately publish and implement final regulations for good manufacturing practices (GMPs)** for dietary supplements, with adequate funding for reasonable enforcement activities. Industry has long sought dietary supplement GMPs from FDA, which DSHEA gives the agency the authority to issue. Yet, a GMP proposal specific to dietary supplements still has not been proposed. Because of unique formulation-related properties of dietary supplements, GMPs for dietary supplements are appropriate to reassure consumers that supplement manufacturers are committed to making products to high quality standards.

- The dietary supplement industry needs to **further expand the use of scientifically based analytical methods for botanicals and other dietary supplement ingredients.** Several organizations are working to develop credible validated methods of ingredient analyses so that consumers are assured that the type and amount of ingredients listed on a label are actually contained in the product. The AOAC International Dietary Supplement Task Force, which includes membership from key officials at FDA, industry and other stakeholders, was organized to create an official compendium of analytical methods for validation of dietary supplement ingredients. Phase I of the project has already begun.

**Benefits**

- **NIH should be given additional resources** to further develop the science to support the benefits and efficacy of dietary supplements. For example, NIH has begun an effort to track the impact of dietary supplements on the health and nutritional status of Americans through the National Health and Nutrition Examination Surveys (NHANES). NIH is also pursuing studies of St. John's Wort for depression, chromium for Type II diabetes and hawthorn extract for congestive heart failure. The Office of Dietary Supplements (ODS) is increasingly viewed as an important center for research and acts as a clearinghouse of information on dietary supplements. ODS is working with the industry to publish the Annual Bibliography of Significant Advances in Dietary Supplement Research.

**Conclusion**

Dietary supplements *are* subject to substantial and dynamic regulation under federal law. CHPA and its member companies are committed to providing consumers with safe and effective products for self-health care and the information to use them wisely. We urge Congress and regulators to resist any suggestion to impose unnecessary and unreasonable restrictions on legitimate products and to support the full implementation of DSHEA, including the appropriation of sufficient resources to enforce the law. Thank you very much for your consideration of our views and concerns on this important matter.

*For further information, please contact Kevin Kraushaar, Vice President & Director of Government Relations or Michael Sargent, Associate Director of State Government Relations at (202) 429-9260.*

John Hathcock, Ph.D.
Vice President, Nutritional and Regulatory Science
Council for Responsible Nutrition
Testimony Submitted to the Senate Subcommittee on
Oversight of Government Management, Restructuring, and the District of Columbia
When Diets Turn Deadly: Consumer Safety and Weight-Loss Supplements
Wednesday, July 31, 2002

Mr. Chairman. My name is John Hathcock and I am the vice president of nutritional and regulatory science for the Council for Responsible Nutrition (CRN). CRN is one of the leading trade associations representing the manufacturers and suppliers of dietary supplements.

I am a nutritional toxicologist with 35 years of professional experience, including tenures as professor at Iowa State University and senior scientist at the Food and Drug Administration. Since joining CRN in 1995, I have authored CRN's *Vitamin and Mineral Safety*, now being updated for the second edition, and continued to publish peer-reviewed scientific articles and make presentations at major national and international conferences on safety and regulatory issues related to foods and supplements. I earned B.S. and M.S. degrees from North Carolina State University and the Ph.D. in nutrition from Cornell University. I am an elected member of the major research-based professional societies in nutrition and toxicology.

Thank you for allowing us to submit our comments for the record with regard to the Senate Subcommittee on Oversight of Government Management, Restructuring, and the District of Columbia's hearing on "When Diets Turn Deadly: Consumer Safety and Weight-Loss Supplements." CRN supports the committee's concerns over the importance of this issue.

The Council for Responsible Nutrition commissioned Cantox Health Sciences International to perform a comprehensive science-based risk assessment on ephedra, and received the Cantox Report in December 2000. The Cantox risk assessment concluded that the dietary supplement ephedra is safe, under the recommended conditions of use, that specify a total daily dosage of 90 mg, divided into smaller doses of up to 30 mg, a six-month continuous use limit, use only by persons 18 years or older, and certain exclusions and contraindications.

The Cantox Report on ephedra evaluated all the available data utilizing a risk assessment method developed by the U.S. National Academies' Food and Nutrition Board. The evidence reviewed included 19 relevant clinical trials, including the data from the now peer-reviewed study conducted by Columbia and Harvard University (Boozer et al.) and published in the *International Journal of Obesity* that found ephedra both safe and beneficial for weight loss.

In reviewing data on both ephedra and ephedrine, Cantox analyzed in detail clinical trials, adverse event reports (AERs) from the Food and Drug Administration (FDA), case

reports and published articles, including data on both human and animal studies. Its exhaustive study revealed no serious concerns dealing with toxicity or other potentially harmful effects. This comprehensive database was analyzed in the context of the U.S. National Academies' Food and Nutrition Board Upper Limit methodology, which is well established, broadly accepted, and generally applicable to dietary ingredients.

Since the release of the Cantox Report, there have been four additional studies released that provided further evidence that ephedra can be safely and effectively used for weight loss under recommended conditions of use, and have reaffirmed the findings of the Cantox Report.

CRN also welcomes the recent announcement by the Department of Health and Human Services of its new efforts to expand scientific research on the safety of ephedrine alkaloids and to aggressively pursue the illegal marketing of non-herbal synthetic ephedrine alkaloid products. CRN has worked with Senators Harkin and Hatch to provide more money in the appropriations process for FDA to increase its enforcement activity with regard to dietary supplements, and for more money to improve FDA's adverse event reporting (AER) system.

CRN believes that it is important that industry and government work together in partnership to continue to examine the relevant science available, and ensure that policies and regulations be based on sound, responsible science.

In addition to complying with all legal requirements, CRN's members adhere to a strict code of ethics, comply with dosage limits and manufacture dietary supplements to high quality standards under good manufacturing practices.

CRN has advocated on behalf of dietary supplements for the last 29 years. We have been the primary association behind the passage of all major dietary supplement legislation since 1976, including the Dietary Supplement Health and Education Act of 1994. We have worked closely and effectively with FDA, Congress and other governmental organizations over the years. CRN supports the authority of, and encourages action by, the FDA to remove from the marketplace any product found to be misbranded, adulterated or contaminated.

Consumers use dietary supplements for a variety of reasons – to complement a specific restricted diet, offset deficiencies in normal diet, aid in disease prevention, and for general health maintenance. Our members are dedicated to providing safe and beneficial products to consumers.

I thank you for your time and consideration. I will be happy to answer any questions you might have. I can be reached at my offices in Washington, DC at 202-263-1024, The Council for Responsible Nutrition at 1875 Eye Street, NW, Suite 400, Washington, DC 20006. www.crnusa.org

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Mr. Chairman and members of the Committee:

Thank you for holding these hearings on a topic of critical importance to the health of the public. The nation has entrusted the Food and Drug Administration with the responsibility of protecting the public from harm caused by problems with its food supply and the medications that they need for good health and well-being. In spite of the FDA's efforts, the public is suffering unnecessary harm and you are serving the public well by asking why this is being allowed to happen.

**Definition of Dietary Supplements**

Because of concern for a healthy diet, the public often turns to dietary supplements to ensure that their diet will contain the nutrients necessary for optimal health. These supplements are intended to replace any missing ingredients, usually vitamins or minerals, and thereby maintain health and "normal" levels of performance. However, many members of the public also desire to have products that improve performance above the levels some might consider "normal." Improved health and performance can be defined in many ways, e.g running faster or even living longer because of freedom from diseases such as heart attacks. Furthermore, to maintain health, the public also needs products that treat or prevent the disorders or diseases of mankind. These are usually considered drugs.

Yet, there is confusion among the public, the medical community and the government regulatory agencies regarding the definitions of foods, dietary supplements, nutritional therapy and drugs. For example, there are different products that prevent a heart attack that are classified either as foods, dietary supplements or drugs. There has been unequal application of the standard of whether a product marketed as a dietary supplement "maintains normal structure and function." Many products are in this "gray" area between foods and drugs depending upon one's definition of "normal." Because these three classifications have major differences in the way they are being regulated by the FDA, the definition has major financial and medical implications. If the products or treatments are harmless, the only considerations would be their expense and whether their use prevents the public from receiving other therapies that could be beneficial. However, many of the substances we take into our bodies can have harm and a risk:benefit ratio must be considered. For drugs, the FDA requires that manufacturers define this ratio before new products can be marketed to the public. However, dietary supplements are treated differently and can be marketed without FDA prior review. For these products the FDA is required to define the risk and can only take action against them when they can prove the product is harmful. These are very different standards and therefore it is essential that the definition of "dietary supplement" vs "drug" is made with care.

**Dietary Supplement VS Drug**

It is essential that a "dietary supplement" be rigorously defined as a substance taken to replace ingredients that are missing or deficient in the diet and therefore

not likely to produce harm. In contrast, the definition of "drug" should be a substance not present in the standard healthy diet that is administered to produce or prevent a change in the state of the body. Even if the change produced is returning the body toward normal, there is the risk that the changes could be beneficial in some but harmful in others. This possibility is fully supported by the wealth of research in recent years that has demonstrated the tremendous variability in response to pharmacologic agents caused by genetic diversity, often called polymorphic (having many forms) responses. Genetic polymorphisms have been found that not only explains why some people fail to respond to a medicine but also explains how opposite responses can occur. For example, differences in DNA sequences in the genes of people can result in a drug causing an increase in heart rate in one and a decrease, or no change, in the other.

**Treatment of Obesity**

The medical community considers obesity as a metabolic disorder that can result in impaired health. The FDA regulates many of the products marketed to treat obesity under the category of drugs because they are intended to prevent the medical complications associated with obesity (heart attacks, strokes, respiratory insufficiency and heart failure). Obesity also can be treated with programs that include diet modification and exercise. These programs often use nutritionally complete products such as Slimfast® to reduce calories AND with exercise to burn excess calories. I do not consider these as dietary supplements but as foods used for dietary exchange.

**Drug Therapy of Obesity**

The FDA has regulated many drug products that act by stimulating that portion of the brain that controls appetite. These drugs are called "adrenergic" because they are chemically related to adrenaline, the natural chemical that is released by the adrenal gland when the body is in a stressful situation. Adrenaline and other adrenergic chemicals that mimic its actions increase heart rate and blood pressure, open the airways to the lungs and cause the person to be more alert and stop seeking food. Excessive adrenaline or administration of drugs with adrenergic effects can cause dangerously high blood pressure in some individuals that can result in heart attacks, strokes and sudden death due to heart rhythm disorders. Excessive effects of these chemicals in the brain can cause nervousness, anxiety, tremor and seizures. Prolonged exposure to high levels of these chemicals can cause aggressive or hostile behavior, addiction and personality changes.

Depending on its chemical structure, an adrenergic substance can cause any number of these actions and the magnitude of any one effect is dependent upon dose or duration of exposure. For example, in a single individual, some drugs in this class will increase heart rate more than other drugs and some decrease appetite more than others. Also depending on the individual, with continued use the effect of these drugs may decrease over time or become intensified.

Individual differences in the structure of the targets (receptors) for these chemicals determine the different responses that a given chemical can produce in a population of people. When millions of people take an adrenergic chemical, there is a broad spectrum of responses. When a large number of people take a mixture of chemicals that all have varying degrees of adrenergic potency, the spectrum of responses is even broader and especially dangerous for some individuals. This is exactly the circumstance in which we find ourselves today. Millions of people with tremendous differences in potential for response are taking a broad spectrum of different chemicals that have adrenaline-like actions.

**Botanicals and Drugs for Obesity**

Several plants have been found that contain chemicals that, when consumed by people, have actions like adrenaline. For centuries, traditional Chinese doctors have prescribed one of these plants of the genus ephedra, ma-huang, to treat asthma and other medical conditions. In the 1940's, US scientists at Eli Lilly extracted a mixture (called ephedra alkaloids) from the plant and isolated one of the most potent chemicals, named ephedrine. Ephedrine is available today in the U.S. by prescription but newer drugs that have fewer side effects have generally supplanted its use. Early in its use it was recognized that ephedrine could cause heart attacks, strokes, nervousness and changes in personality. It was also found to produce a sense of well-being, energy and a feeling of euphoria or "high." These actions and risks are mentioned in every credible pharmacology textbook or medical reference source and not debated by the medical or scientific community. Over the last fifty years, chemists and pharmacologists have experimented with chemicals structurally related to ephedrine, e.g. amphetamine, dextro-amphetamine, methylphenidate (Ritalin®), methamphetamine or "speed," phenylpropanolamine (PPA), fenfluramine and more recently sibutramine. All of these agents have been found to decrease appetite but they also increase heart rate and blood pressure. All but the more recently developed agent sibutramine have been found to cause the same side effects as ephedrine. With further study, even sibutramine is now being looked at with concern because of recent reports of strokes. Many of these drugs also were found to be harmful and addictive and are treated as illegal with criminal penalties for their possession or sale. Fenfluramine, a component of the popular Phen-fen, was removed from the market because of cardiac toxicity. Phenyl propanolamine, a component of several products for allergic symptoms or weight reduction, was removed from the market because of a large study that documented its ability to cause strokes. Because ephedrine can easily be chemically converted to these illegal drugs, possession of large bulk quantities is a criminal offense.

The pharmacologic data are very consistent and conclusive: if large numbers of people are exposed to even relatively small amounts of these chemicals, they can cause serious medical complications in some susceptible individuals or in all people at excessive dosages. This is further substantiated by the results of research with another class of drugs in hundreds of thousands of patients with

heart disease: drugs that BLOCK the actions of adrenaline REDUCE the risk of heart attacks and strokes. Objective evaluations by scientists fully knowledgeable of the pharmacology of ephedrine have concluded that products containing ephedrine will carry the risk of catastrophic cardiovascular or neurologic events.

**Ephedrine/Caffeine Combinations**
Many of the ephedrine containing products marketed as dietary supplements also contain caffeine that makes them even more dangerous. Caffeine, although weaker than ephedra, also stimulates the heart, brain and blood vessels producing the same effects as adrenaline but, because it works by a different mechanism, the effects are likely to be more intense in the presence of ephedrine or other adrenergic drugs.

**Clinical Research in Obesity**
The manufacturers of ephedrine-containing products and ephedra/caffeine combinations for weight loss have claimed that their products can lower body weight and that this will result in better health. This is a medical claim for the treatment of obesity, not a claim of a dietary supplement. Therefore, these products should be regulated as drugs and removed from the market until such time as the manufacturers demonstrate that they are safe and effective as a medication.

The manufacturers of these products have conducted short-term trials, often demonstrating small reductions of body weight. The longest, and perhaps the best, of these trials was a six month study by Boozer and colleagues (Int. J. Obesity, 26:593, 2002). This study is often misrepresented as a demonstration of how safe and effective an ephedra/caffeine combination product might be. In fact, it demonstrates just the opposite. In carefully screened subjects under medical supervision, it found a mean reduction of only 11 pounds in 83 subjects that varied between individuals from 0 to 22 pounds. As expected, the subjects had an increase in heart rate and blood pressure and the expected side effects of ephedrine-containing products. However, the most important observation was that 31 of the 284 subjects screened for the study were excluded because the investigators were concerned that they had medical conditions that made taking ephedra/caffeine products inappropriate or dangerous. The authors, the editor of the journal (Dr. Atkinson) and Dr. Dulloo in an accompanying editorial caution the public that these products should only be used as they were in this trial, under medical supervision. The editorial recommended that these products be available only by prescription.

**Scientific Standards for Certainty**
The industry has questioned the "scientific methods" used by those who conclude that these products are dangerous for the public. For that reason, I will review my credentials as a scientist and why I was asked by the FDA to provide a scientific analysis of the data on these products. In 1995 I was asked to serve

as a consultant to the Center for Food Safety and Nutrition of the Food and Drug Administration because of a concern over the number of severe adverse reactions reported to the Agency. I believe I was asked to serve as a consultant because of my training in experience as a clinical pharmacologist. I obtained a PhD in pharmacology, the study of the actions of drugs, in 1967. After working for a pharmaceutical company for a few years, I left to study medicine at the University of Miami and then trained in Internal Medicine at Vanderbilt. After Board Certification in Internal Medicine, I spent an additional two years to train in the subspecialty of clinical pharmacology, the study of the actions of drugs in humans. I remained on the faculty at Vanderbilt and rose to the rank of Professor of Medicine and Pharmacology before moving to Georgetown to Chair the Department of Pharmacology. I am now Vice President for Health Sciences at the University of Arizona. Over the last 35 years, I have studied the actions of drugs. I have been asked to serve as an advisor to the NIH, the FDA, the DOD and dozens of pharmaceutical companies on the actions of drugs in humans. My experience has been punctuated with events that have given me a perspective and an expertise in the toxicity of drugs. The first was the opportunity to serve as co-director of the NIH-sponsored Cardiac Arrhythmia Suppression Trial that found that drugs designed to save lives were actually causing thousands of deaths each year. The second major experience was to serve as leader of the team that detected the mechanism of cardiac toxicity caused by terfenadine (Seldane®) contributed to its ultimate removal from the market. As director of the Center for Education and Research on Therapeutics at Georgetown and now at Arizona, I lead a team of scientists who are studying the more than 50 marketed prescription drugs that have the potential to induce life-threatening arrhythmias.

For these reasons, I was asked to be a consultant to the FDA and review 140 reports of adverse events related to the use of dietary supplements containing ephedra alkaloids that were submitted to the FDA between June 1, 1997, and March 31, 1999. The following is the conclusion of my report: *"The occurrence of serious side effects makes the use of ephedrine containing products as dietary supplements at dosages that can increase blood pressure and heart rate in susceptible individuals unacceptable without medical supervision."* A analysis of these same cases was published by another FDA consultant, Dr. Neil Benowitz, in the New England Journal of Medicine 343(25):1833, 2000. These authors concluded that "*The use of dietary supplements that contain ephedra alkaloids may pose a health risk to some persons."* Of course, one can always be in doubt about the causation of rare events when analyzing a single report. However, we must consider the totality of evidence for scientific validity and consistency. The inevitable objective conclusion is that the use of these products causes a serious health risk to the public. Decades of experience summarized in textbooks of medicine and pharmacology support this conclusion. Many agencies and regulatory bodies such as Health Canada have already taken action to protect the public.

**Recommendations**
In summary, I strongly encourage you to enact legislation that will more accurately distinguish between drugs and dietary supplements and clarify how the FDA should regulate these products. Many of the products that are marketed as dietary supplements and especially the ephedrine-containing products are in fact drugs because they are not normal constituents of a healthy diet and they are being used and promoted as medicines for weight loss. Without medical supervision these products present a clear and serious danger to the public and should be banned for use without a prescription. The available evidence clearly shows that these products have harm in some individuals that, without medical supervision, cannot be prevented by warning labels. As many as 10% of patients will have medical conditions that place them at increased risk of adverse effects. I hope you will take swift action to protect the public.

Thank you for the opportunity to provide this statement for the record.

Raymond L. Woosley, MD, PhD

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